INSIDE THE CELL

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Written by Maya Pines (1979)
Revised by Anne A. Oplinger (1989)
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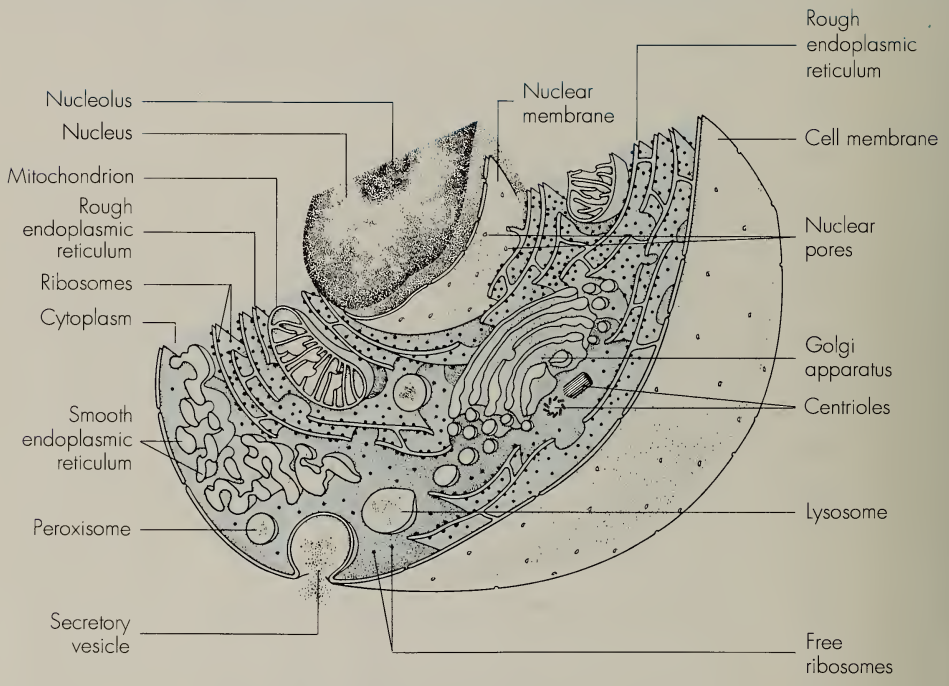
This drawing of an idealized animal cell is based on photographs taken with powerful electron microscopes. Within the cell's membrane are such organelles as the mitochondria (energy producers), the rough endoplasmic reticulum (a site of protein production), the Golgi apparatus (a protein sorter), and the largest organelle, the nucleus (which contains the hereditary material DNA). In addition to these organelles, cells also contain an elaborate network of protein filaments called the cytoskeleton (not shown here) that anchor the organelles, maintain the cell's shape, and direct intracellular traffic.



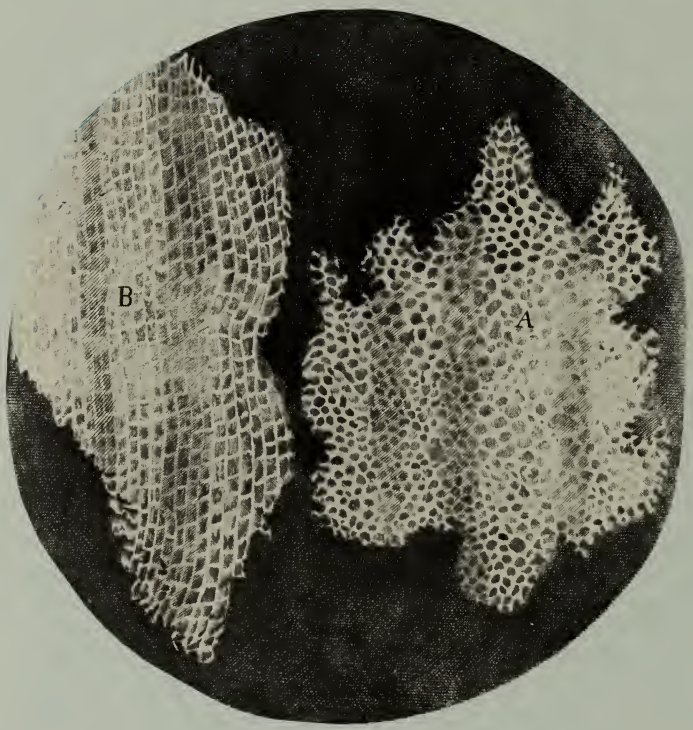
THE NEXT BIG LEAP

The next big leap in medicine may occur as researchers increasingly apply what they have learned about the world of the living cell to the problems of disease. Although many of the features of cells have been scrutinized and are now quite familiar to students of biology, scientists still want to know more about the architecture of cells, as well as how cells move and grow, how they communicate with one another, and how they work—or fail to work. As scientists study cells in finer and finer detail, the relationship between cell malfunction and certain diseases becomes clearer. Cancer, for instance, is a derangement of cell growth. Normal cells stop dividing upon contact with other cells, but cancerous cells multiply endlessly, as if their surface membranes can no longer perceive signals from nearby cells. If the still-cryptic signals that tell a cell when to divide and when to stop are deciphered, new approaches to cancer treatment could result. Other major health problems of today, including genetic disorders, heart disease, and diabetes, may also yield to improved therapies as more is learned about the cell.

The work is already under way. In the past 40 years, through a combination of electron microscopy, biochemical analyses of cell parts, X-ray crystallography, and other techniques, cell biologists have looked inside the cell and revealed it to be a complex and highly organized entity. A typical cell is like a miniature body containing tiny organs, called organelles. One organelle is the command center, others provide the cell with energy, while still others manufacture proteins and other molecules that the cell needs to survive and to communicate with the world around it. The entire cell is enclosed in a fine skin, its surface membrane. This membrane not only keeps the cell intact, it also provides portals that allow selected molecules into and out of the cell.

This booklet describes the internal landscape of the cell and the work of some of the pioneers who first mapped its features. Much has been glimpsed, but much more remains to be seen. How, for instance, is the work of protein manufacture orchestrated within the cell? What prompts a cell to divide? How does a human being, complete with eye, hair, bone, blood, skin, and nerve cells, arise from a single undifferentiated cell? Solving these cellular mysteries will require the concerted efforts of scientists from many disciplines, including anatomy, physiology, physics, and chemistry. Cell biologists of today can look forward to a future of discovery and refined understanding as they continue to reveal the living worlds within us.

This drawing of cork tissue, as seen under a simple microscope, appeared in Robert Hooke's 1667 book, *Microscopy*. Hooke named the compartments "cells."



WHAT ARE CELLS?

The idea that every living thing is made up of cells emerged from an encounter between two German scientists in 1838. Nearly two centuries earlier, in 1665, the English physicist Robert Hooke looked at a sliver of cork through a microscope lens and noticed some "pores" or "cells" in it. Hooke believed the cells had served as containers for the "noble juices" or "fibrous threads" of the once-living cork tree. He thought these cells existed only in plants, since he and his scientific contemporaries had observed the structures only in plant material.

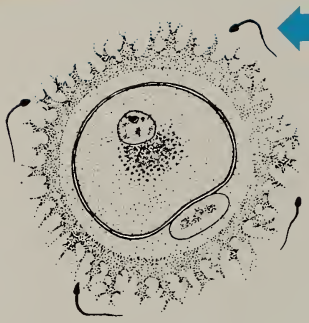
During a dinner conversation in 1838, however, the botanist Matthias Schleiden, who had been studying plant cells, and the zoologist Theodor Schwann, who had been examining the nervous tissue of animals, realized that the similarities between the structures they had been investigating were too strong to be accidental. In 1847, Schwann wrote a paper describing how all animal tissue, including bone, blood, skin, muscle, and glands, is composed of cells. Even sperm and eggs are cells. Schleiden elaborated on this idea as it applied to plants. A German pathologist, Rudolph Virchow, is given credit for being the first to state, in 1858, what became known as the cell theory: "Every animal appears as a sum of vital units, each of which bears in itself the complete characteristics of life."

The cell theory united plant and animal sciences by recognizing that the cell is the fundamental component of all living organisms, from orchids and earthworms to human beings. It provided an intellectual framework that revealed the hidden similarities of form and function in extremely diverse organisms, and it gave scientists a way of making sense out of the bewildering array of living creatures. But what is a cell?

Obviously, there are major differences among cell types. Muscle cells, which can contract, have to be quite different from liver or bone cells. Nerve cells have long, thin fibers that, in humans, might extend more than 3 feet from the spinal cord to the toes, while blood cells have no projecting fibers at all. Plant cells have a unique ability to use light for energy.

Then what do all these cells have in common? Discovering their shared properties was difficult. At first, scientists thought that the cell was just a blob of jelly, or some primordial soup enclosed in a bag. They named the jelly "protoplasm." For a long time they could not find anything in the protoplasm, which later became known as the "cytoplasm."

Part of the difficulty in studying cells, of course, is due to their extremely small size. The cells of multicellular organisms are impossible to see with the unaided eye. Schleiden and Schwann, like cell biologists before and after, relied upon microscopes to enlarge the image of cells so that they could be studied. Microscopes employ one or more curved lenses and a



Egg cell

Sperm cell

The variety of human cells. After fertilization by a sperm, a single human egg cell divides again and again into many kinds of specialized cells whose structures vary according to the functions they fill. Some nerve cells, for example, are 3 feet long to reach from spine to toe. The orderly structure of typical skeletal muscle is shown here in such detail that if the entire muscle cell were drawn to the same scale as the fragment shown, it might be 1,000 feet long.

Muscle cell

Rod cell in eye

Hair cell

Nerve cell

Anton van Leeuwenhoek (1632-1723) was an early microscopist who ground his own lenses as a hobby and was the first to observe such living cells as sperm and pond water microorganisms.

source of illumination (typically white light) to magnify cells.

One of the most remarkable early microscopists was a Dutch draper named Anton van Leeuwenhoek, who ground his own lenses as a hobby. Van Leeuwenhoek, who once made a lens from a grain of sand, used simple (single-lensed) microscopes to examine everything from pond water to the scum on his teeth.

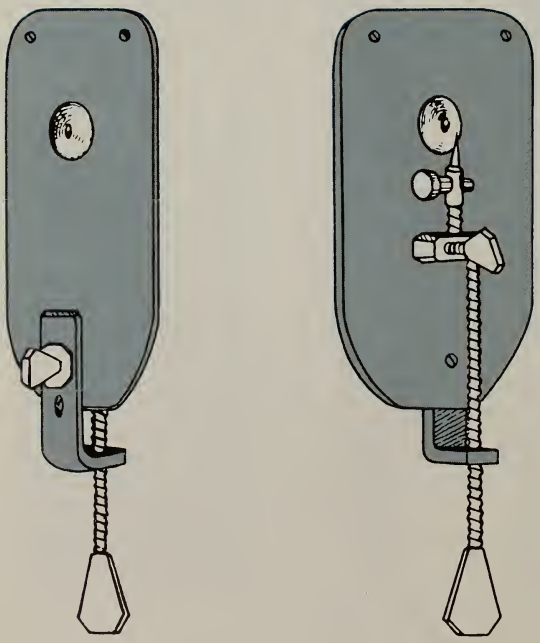
In 1702, van Leeuwenhoek reported to the Royal (Scientific) Society of London that he had observed "a little clear sort of light in the middle" of a fish blood cell he had been examining. This description of what was later called the cell's nucleus was the first suggestion that animal cells had an internal structure. Throughout the 18th and 19th centuries, improvements in microscopes and techniques for selectively staining cell parts enabled cell biologists to distinguish other particles within the cell. However, researchers could not study these minute flecks in detail because they met an insuperable obstacle: the wavelength of light.

A light microscope—even one with perfect lenses and perfect illumination—simply cannot be used to distinguish objects that are smaller than one-half the wavelength of light. White light has an average wavelength of 0.55 micrometers, half of which is 0.27 micrometers. (One micrometer is a thousandth of a millimeter, and there are about 25,000 micrometers to an inch. Micrometers are also called microns.) Any two

lines that are closer together than 0.27 micrometers will be seen as a single line, and any object with a diameter smaller than 0.27 micrometers will be invisible—or, at best, show up as a blur.

Although the nucleus of a typical human cell is relatively large (about 7 micrometers in diameter), most organelles vary from a width of only 1 micrometer to structures so fine that they must be measured in nanometers (which are 1,000 times smaller than micrometers), or even in angstrom units (10 times smaller than nanometers). To see such tiny particles under a microscope, scientists must bypass light altogether and use a different sort of "illumination," one with a shorter wavelength.

The invention of the electron microscope in the 1930's filled the bill. In this kind of microscope, electrons are accelerated in a vacuum until their wavelength is extremely short—only one hundred-thousandth that of white light. Beams of these high-speed electrons are focused on a cell sample and are absorbed or scattered by the cell's parts so as to form



This is the actual size of a typical microscope built by van Leeuwenhoek. He peered through the tiny lens opening on one side of a metal plate (left) to see the specimen mounted on the point of a pin on the other side (right). The specimen could be moved into focus by a system of screws.

an image on an electron-sensitive photographic plate.

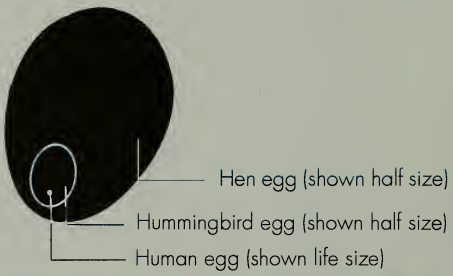
If pushed to the limit, electron microscopes can resolve objects as small as the diameter of an atom. Most electron microscopes used to view biological material can "see" down to about 10 angstroms—an incredible feat, for although this does not make atoms visible, it does allow researchers to distinguish individual molecules of biological importance. In effect, it can magnify objects up to 1 million times. Nevertheless, all electron microscopes suffer from a serious drawback. Since no specimen can survive under their high vacuum, they cannot show the ever-changing movements that characterize a living cell.

The first electron microscopes were used to study crystals and were impractical for the study of cell structure. Cell researchers had to learn how to cut extremely thin slices of cells, sometimes down to a thickness of only a few hundred angstroms, so that electrons could pass through them. Also, to ensure contrast between different parts of the otherwise transparent cell, new staining techniques had to be devised, involving "heavy" metals that are absorbed to differing extents by various cell parts. The cell sections also had to be "fixed" in new ways, to preserve them, and embedded in new kinds of materials (mostly transparent plastic). Altogether, it was not until the early 1950's that electron microscopes began to be used routinely. While microscopists were looking through their instruments at smaller and smaller particles in cells and attempting to understand their structure, another group of scientists was pursuing an entirely different, but equally important, line of research—biochemistry.

Unit	Equal to	Used to Measure
Centimeter	1/100 meter	Objects visible to the eye
Millimeter	1/10 centimeter	Very large cells
Micrometer (or micron)	1/1000 millimeter	Most cells, large organelles
Nanometer	1/1000 micrometer	Small organelles, large molecules
Angstrom	1/10 nanometer	Molecules, atoms

Units of size commonly used in cell biology.

The size of common objects as viewed under microscopes.



Shown as if magnified 100 times

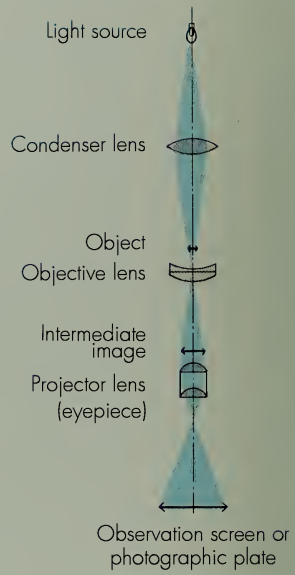
Human egg superimposed on amoeba

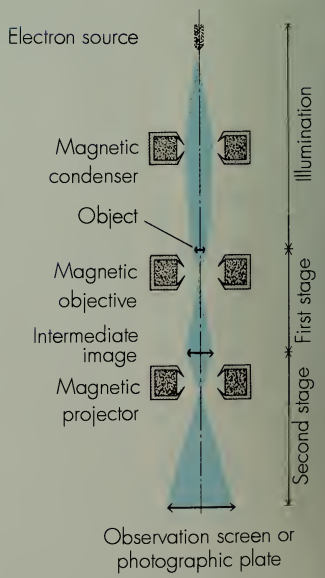
- Human liver cell
- Influenza bacillus

Shown as if magnified 10,000 times

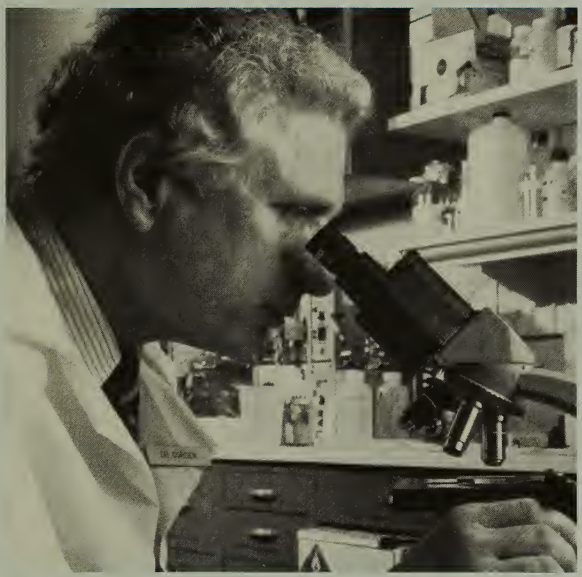
- Pneumococcus bacterium
- Hemoglobin molecule

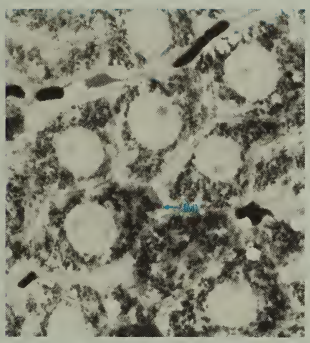
Diagrams of the parts of a light microscope (top) and an electron microscope (bottom).

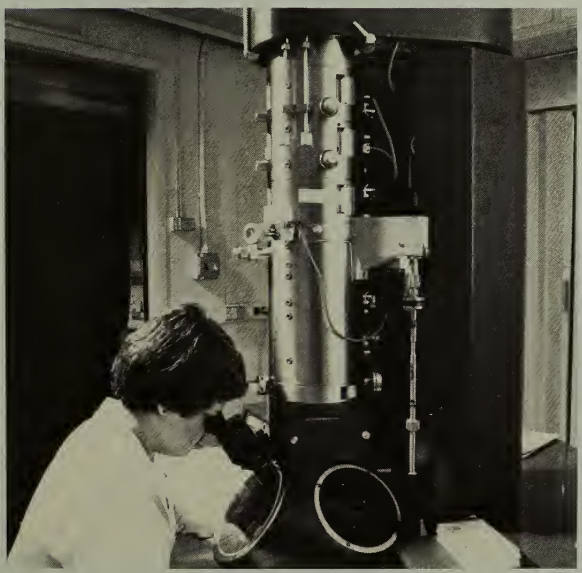


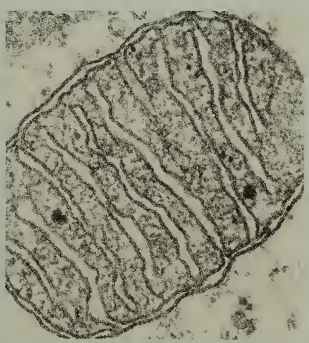


With a light microscope (left), a viewer can see several cells and the organelles they contain (arrow indicates a mitochondrion), while an electron microscope (below left) allows a user to see objects of interest (in this case a mitochondrion) in much greater detail.









Modern Microscopy Gives Clear View of Cell Structure and Movements

Using an instrument the size of his palm, Anton van Leeuwenhoek was the first person to study the movements of living sperm. Modern descendants of van Leeuwenhoek's light microscope can be over 6 feet tall, but they continue to be indispensable to cell biologists because, unlike electron microscopes, light microscopes enable the user to see living cells in action. The primary challenge for light microscopists since van Leeuwenhoek's time has been to enhance the contrast between pale cells and their paler surroundings so that cell structures and movement can be seen more easily. Recently, ingenious strategies involving video cameras, polarizing light, digitizing computers, and other techniques have yielded vast improvements in contrast and have fueled a renaissance in light microscopy.

A polarizer causes light waves to move in parallel planes, thus reducing the distortion that results when light scatters across a magnified object. This technique was first used in the 1950's, and provided many new clues to cellular activities, particularly the intricacies of cell division. Further enhancements in visualizing the cell's interior came in the early 1980's when microscopists Shinya Inoué of the Marine Biological Laboratory in Woods Hole, Massachusetts, and Robert Allen of Dartmouth College began turning video cameras onto living cells. Unlike the eye, a video camera can "see" objects clearly even when the contrast between subject and background is very poor. Inoué and Allen used video cameras to watch food-containing vesicles and other bodies in the cell move rapidly along slender track-like organelles. Video images can now be further enhanced by digitizing computers, which, when attached to a camera, scan the cell, break down the image into light and dark bits, and then reconstruct the image so that "visual noise" (grayness) is subtracted, while objects of interest are highlighted.

A new type of microscope, called the confocal microscope, promises to have a great impact on the study of cell structure. A confocal microscope passes a beam of light over a tiny portion of a cell, then focuses the light that reflects off the specimen through a pinhole. A sharply focused, three-dimensional image of a cell or cell structure can be built up by recording the intensity of the light beam coming off each scanned point and then reconstructing the whole image on a viewing screen. Because confocal microscopes can be used on living cells, they allow researchers to see clearly cell movements and the interactions of neighboring cells.

Electron microscopy is also undergoing some exciting developments. One new instrument that has aroused great interest is the scanning tunneling electron microscope. This device consists of an ultrathin tube that is held a fraction of a millimeter away from a cell or other sample. The distance between the sample and the tube is reduced until a current of electrons jumps from the sample and travels up the tube, a phenomenon called tunneling. As the tube is moved over the surface of the sample, a computer records the distances between the sample and the tube and converts this information into a picture of the sample's contours. In 1989, researchers reported using scanning tunneling electron microscopy to obtain, for the first time, direct images of pure DNA. Eventually, this method may be used to observe living viruses or the actions of molecules on the cell surface. While these latest revolutions in microscopy are still in their early stages, they are already enabling scientists to see the tiniest details of cell structure and activity in ways undreamed of a few years ago.

A FRUITFUL FUSION OF TWO TECHNIQUES

The study of biochemistry goes back to Antoine Lavoisier, the 18th-century French scientist who explained the role of oxygen in the respiration of both plants and animals, established the composition of water and other compounds, and introduced quantitative methods in the study of chemical reactions, thereby laying the foundation for modern chemistry.

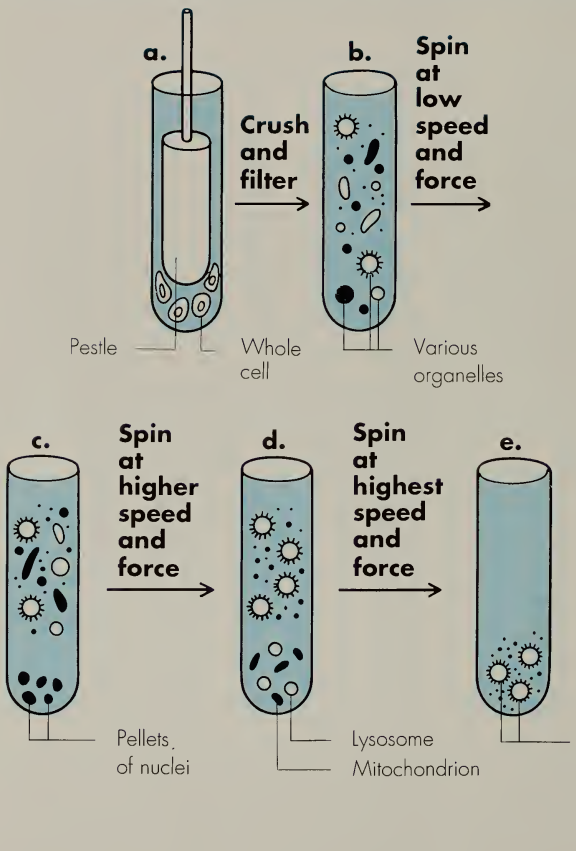
In the 19th century, biochemists isolated and identified many cellular chemicals—for example, hemoglobin, the red pigment of blood, and chlorophyll, the green pigment in plants. They discovered that compounds taken from animal tissue consisted of the same chemical elements as nonliving materials. They isolated the nucleic acids, which are now known to govern heredity and protein synthesis. They began to study proteins, especially enzymes, which catalyze chemical reactions in cells.

When dealing with cells, biochemists behave quite unlike microscopists, who have enormous respect for the details of the cell's structure. Biochemists simply grind up large quantities of cells to release their contents into a solution (this is called "homogenizing") and then analyze the mixture (called the homogenate). Often, the homogenate is fractionated, or separated, into individual components. Usually this is done with a centrifuge, a machine that separates particles according to their size and density by whirling them around at varying speeds. The heaviest and largest particles are thrown to the bottom of the test tube most rapidly, followed by somewhat lighter and smaller components, until at the highest speed there remain only the smallest and lightest particles at the top.

In 1925, a Swede, Theodor Svedberg, developed an instrument that would prove at least as revolutionary as the electron microscope: the ultracentrifuge, a machine that could spin its samples at such high speeds and with such force (it could attain hundreds of thousands of times the force of gravity) that many of the smaller and lighter components of the cell and even proteins and nucleic acids could be collected separately and studied for the first time.

The significance of this new instrument did not become apparent until years later. For a long time, biochemists seemed interested only in the chemical reactions of the cell as a whole—for example, how the cell obtains energy or synthesizes proteins. The scientists gave little thought to what the various fragments they dealt with represented in the cell—what they looked like, how they were organized, or how they related to one another. Very often, biochemists gave these fragments names of their own, unaware that microscopists had already examined and named them.

"There were two classes of people, and they didn't communicate with each other at all!" recalls DeWitt Stetten, Jr., Deputy Director for Science, Emeritus, at the National Institutes of Health (NIH). Finally, in the 1950's, the two groups began to



How a centrifuge is used to isolate cell components. To separate the various particles in cells, biochemists begin by placing whole cells in a solution and then breaking the cells with a pestle or with high-frequency sound waves (a). The mixture is then filtered to remove unbroken cells. At this point, the cell organelles and fragments are free-floating (b). As the sample is spun in the centrifuge at increasingly higher speeds and force, the organelles begin to settle to the bottom depending on their size and density. First to settle out are pellets of nuclei (c). At forces greater than 10,000 times that of gravity, pellets of mitochondria and lysosomes sink to the bottom (d). Finally, at very high speeds and at forces 100,000 times that of gravity, the very lightest particles and organelles begin to settle out (e).

edge closer together. "It was an important fusion," says Stetten. By that time, electron-microscopic techniques had been refined. When the microscopists discovered that the biochemists' particles matched what they had been seeing under their microscopes, and the biochemists learned that the microscopists could actually see what they had been analyzing, there was great rejoicing on both sides.

As the microscopists and biochemists began to communicate, there was an avalanche of discoveries about the world within the cells of animals and plants. A whole new vocabulary had to be developed for the cellular structures that the electron microscope and ultracentrifuge uncovered. Now, after 40 years of painstaking investigation, cell biologists have defined many of the general characteristics that cells share, and have discerned the mechanisms that cells use to make enzymes and other vital molecules.

Enzymes—The Catalysts of Life

Without enzymes, there would be no life. Nearly all of the myriad chemical reactions occurring within a cell at any moment require the participation of at least 1 of the 4,000 or so enzymes in the cell's repertoire. Many cellular processes are energetically unfavorable; without enzymes they would proceed slowly or not at all. Enzymes act as catalysts, speeding up reactions without being permanently altered themselves. Thus, enzymes can do their jobs—often, cutting apart or splicing together other molecules—over and over. According to chemist Ronald Breslow of Columbia University, enzymes work so well that a process that takes 5 seconds (such as reading this sentence) with enzymes would take 1,500 years without them. Enzymes also have great specificity; like a lock, each enzyme will accept only appropriately shaped "keys" (called substrates).

With few exceptions, enzymes are proteins and are made of strings of amino acids ordered according to instructions contained in the genes. Even if the sequence of amino acids in an enzyme is known, however, scientists cannot predict how the enzyme will fold into its final, active shape. This is the so-called "folding problem" that many researchers are working to solve. If scientists can learn the rules by which enzymes and other proteins fold, it would open the way to synthesizing engineered, artificial enzymes with therapeutic, industrial, and manufacturing applications.

The first exception to the rule that all enzymes are proteins was uncovered in the early 1980's when Thomas Cech of the University of Colorado at Boulder and other scientists made the startling discovery that the nucleic acid RNA can act as an enzyme because it can cut and splice itself. This observation, which led, in 1989, to a Nobel Prize for Cech and Sidney Altman of Yale University, has caused some scientists to speculate that RNA was the first self-forming and self-reproducing molecule to evolve.

If an enzyme is missing or malfunctioning, one of a large class of diseases, collectively called metabolic disorders, may develop. To date, most attempts at treating such diseases in humans with enzyme replacement have failed because the body quickly breaks down ingested or injected enzymes. In 1987, however, researchers at Duke University developed a chemically "camouflaged" enzyme that can escape detection by the antibodies that attack foreign molecules. It has shown promise in treating children who are deficient in adenosine deaminase, an enzyme that plays a crucial role in the immune system.

THE ASTONISHING UNIFORMITY OF LIFE

All cells—whether from a bacterium, plant, mouse, or human—are made of the same basic materials: nucleic acids, proteins, carbohydrates, water, fats, and salts.

"The uniformity of the earth's life, more astonishing than its diversity, is accountable by the high probability that we derived, originally, from a single cell," notes physician Lewis Thomas in *The Lives of a Cell*. "It is from the progeny of this parent cell that we take our looks; we still share genes around, and the resemblance of the enzymes of grasses to those of whales is a family resemblance."

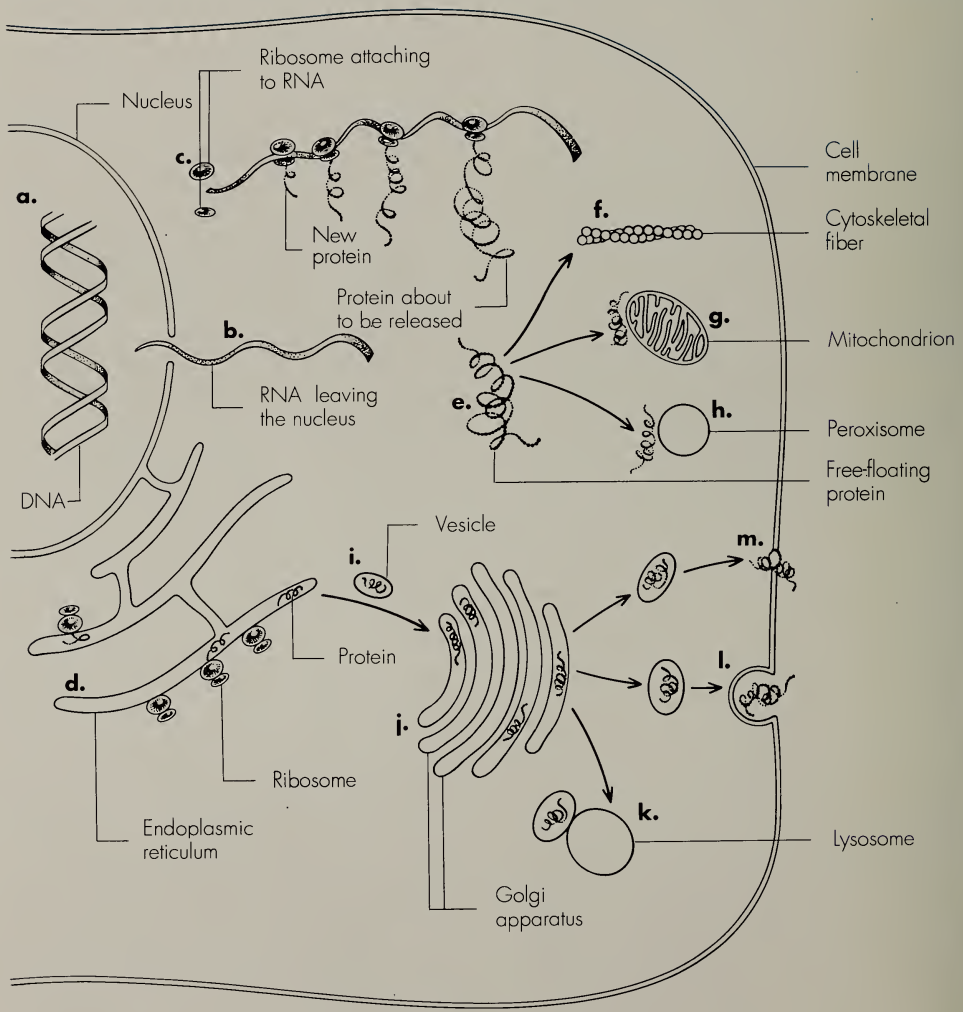
The genetic material in all these cells is deoxyribonucleic acid (DNA), a large molecule that directs the making of duplicate cells. DNA also directs the building of proteins according to a complex code. Even the simplest living cells—the mycoplasma—contain a relatively large amount of DNA, enough to code for up to a thousand different proteins. Every human cell has about 6 feet of very tightly wound DNA strands contained within its nucleus, and every adult carries about 100 billion miles of ultrathin DNA strands in his or her body—a distance greater than the diameter of the solar system.

Each cell is separated from the rest of the world by a membrane so thin that it cannot be seen under a light microscope. Despite its ethereal nature, the surface membrane is exceedingly powerful, controlling everything that goes into and out of the cell and relaying vital messages. Similar membranes enclose or make up a large number of the cell's organelles.

There is a fundamental distinction between the two major categories of cells. Prokaryotic cells, which include bacteria, mycoplasma, and blue-green algae, do not have a membrane around their nuclear region. Eukaryotic ("proper nucleus") cells, in contrast, have a double membrane separating the nucleus from the cytoplasm, as well as many other internal membranes to segregate their organelles. The cells of all animals and plants (except blue-green algae) and one-celled protozoa are eukaryotes.

Only eukaryotic cells are able to combine with one another to form multicellular systems—an important step up the evolutionary ladder. And while, in general, prokaryotic cells produce only exact duplicates of themselves, eukaryotic cells are capable of differentiation into many kinds of cells, at least in higher organisms. This gives eukaryotic cells certain obvious advantages. However, prokaryotes have advantages of their own: simpler nutritional requirements and much more rapid growth and division. As Daniel Mazia of Stanford University points out, the differences between the two types of cells are simply "different ways of making a living." A cell's job—which, for many cells, centers on the manufacture of proteins—is divided into many steps. In eukaryotes, the production of protein begins in the most prominent organelle—the nucleus.

Protein production begins in the nucleus at the DNA (a). A coded message for a protein leaves the nucleus in the form of RNA (b) and goes to either free ribosomes (c) or to ribosomes bound to the endoplasmic reticulum (d). •When released from a free ribosome, a protein (e) can become incorporated into cytoskeletal fibers (f) or into such organelles as a mitochondrion (g) or a peroxisome (h). Proteins made in the endoplasmic reticulum leave in a vesicle (i) and migrate to the Golgi apparatus (j). Proteins are sorted in the Golgi and are then carried in vesicles to lysosomes (k), or are secreted (l) or incorporated into the cell's surface membrane (m).



THE NUCLEUS, THE CELL'S "COMMAND CENTER"

The nucleus is the biggest, densest, most obvious structure in the eukaryotic cell—the first to be recognized by microscopists and the first to be isolated in the biochemists' centrifuge.

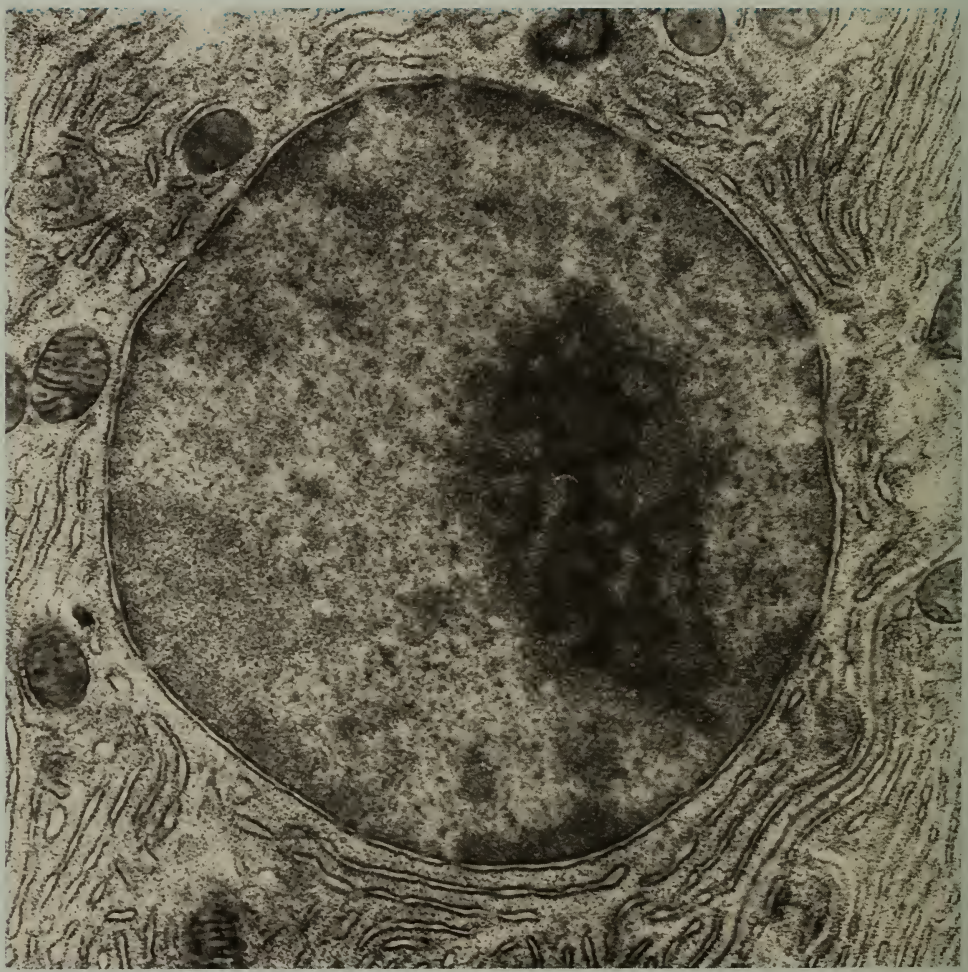
For many years, nobody knew what the nucleus did. In the 19th century, several researchers noted that before a cell divided, the nucleus divided. But it was not until the beginning of the 20th century that scientists grasped the connection between the rodlike chromosomes (tightly packed bundles of DNA and protein) that had been observed in the nucleus and the transmission of hereditary traits. At that point, the importance of the nucleus became clear.

The nucleus is the cell's command center. The chromosomes contain the genes (made of DNA) that give directions for everything the cell is and will be, and thus control the cell's reproduction and heredity. DNA is a deceptively simple molecule, consisting of a sequence of subunits, called bases, linked together to form a double helix that can be visualized as an immensely long, corkscrew-shaped ladder. Each rung in the ladder is made up of two bases fitted together, and the ends of the rung are attached to chains of sugar-phosphates that are like the upright rails of a ladder. A unit of DNA containing one sugar molecule, one phosphate molecule, and one base is called a nucleotide. There are only four different bases: adenine (A), thymine (T), guanine (G), and cytosine (C). They pair with each other so that A is always opposite T and G is always joined to C. Thus, the sequence of bases on one side of the ladder (for example, AGCGT) is complementary to, and determines, the sequence on the other side (TCGCA). This is the "genetic alphabet"—a small set of "letters" with which, as with the ABC's, an infinite number of messages can be written.

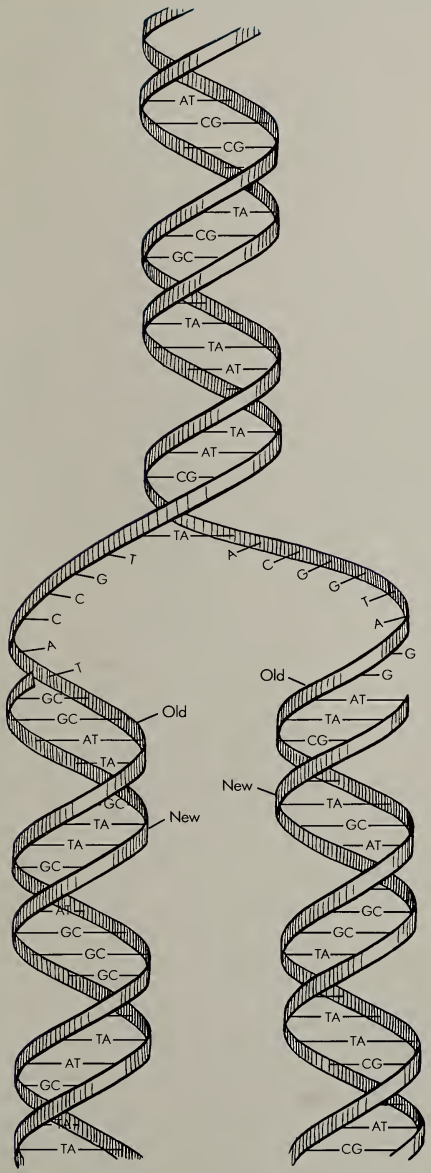
As might be expected, the nucleus is constantly active. Before cell division, all of the information contained within the DNA must be duplicated, in a process called replication. The speed with which replication occurs is astonishing. For example, before a single *Escherichia coli* (a common intestinal bacterium) splits in two, which it does every 20 minutes, the 360,000 turns of its DNA helix must first be unwound. Next, each of the 3.6 million nucleotides on one side of the DNA molecule pulls away from its mate. As the molecule "unzips," each half serves as a mold, or template, for a new molecule. In a matter of minutes, a total of 7.2 million "free" nucleotides are brought to each template and attached A to T and G to C. Finally, each new double strand retwists itself into a helix. (In prokaryotes, such as *E. coli*, the helical DNA exists as a single ring floating in the cytoplasm and does not condense into separate chromosomes.)

All of this molecular maneuvering must be performed both rapidly and accurately. If nucleotides are lost, rearranged, or erroneously paired, the garbled instructions that result could lead to a nonfunctioning protein when the DNA's code is translated.

The nucleus, where the genetic material DNA is stored, is the cell's largest organelle. It is surrounded by a double membrane that is permeated with "gates" called nuclear pores, which may be the routes by which genetic messages pass into the cytoplasm. The nucleolus is the site of ribosome manufacture.



To replicate before cell division, the DNA double helix separates and unwinds and each strand acts as a template for the formation of a mirror image according to the rules of base pairing: A with T, and G with C. This results in two daughter DNA molecules whose sequences are identical to those of the original DNA.



After replication in human cells, DNA condenses into 46 pairs of chromosomes. At this point, the membrane surrounding the nucleus breaks down, and the chromosome pairs pull apart and move to the poles of the cell. Then the cell divides, forming two identical daughter cells, each with 46 chromosomes. The production of germ cells, or sperm and eggs, is a more complex process in which a second division of the nucleus occurs, resulting in cells that have 23 chromosomes each, instead of 46. When an egg is fertilized by a sperm, the complete complement of 46 chromosomes is restored.

Each of us begins as a single, fertilized cell, a microscopic package that contains within the DNA directions for everything that we can become. The single cell then divides again and again. As Mazia puts it, the story of the cell cycle is "double or nothing. With few exceptions, a living cell either reproduces or dies; the principle is so simple that no one has bothered to call it a principle. A cell is born in the division of a parent cell. It then doubles in every respect: in every part, in every kind of molecule, even in the amount of water it contains."

Some of our cells are very short-lived. Scavenger white blood cells, for example, circulate and consume invading particles for only a few days before they die. In contrast, our brain cells never reproduce. Most live as long as we do, but when one dies, it is not replaced.

At any instant, only certain genes in

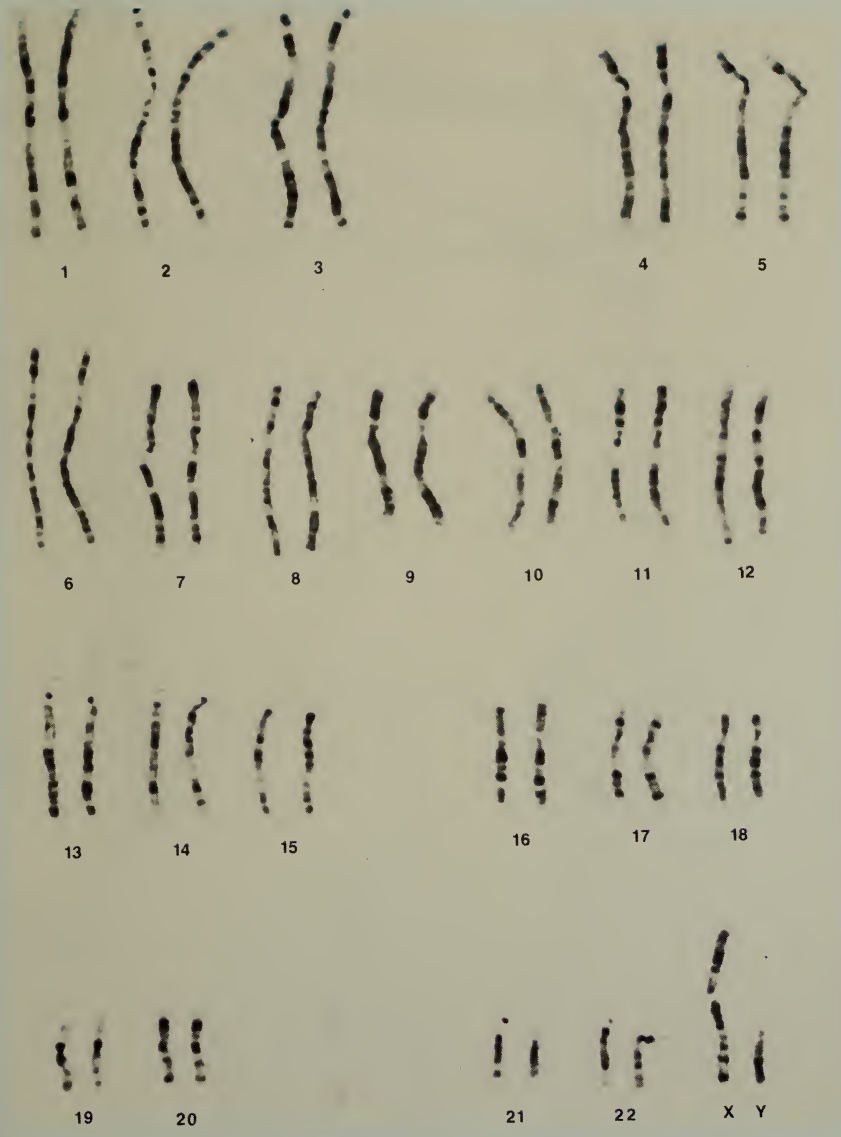
a cell are "on," or "expressed," and giving orders for the production of specific proteins. Some of the instructions that switch these genes on or off come from the cytoplasm, where they are generated as a result of interactions between the surface membrane and the environment. Thus, the commands from the nucleus are influenced by what goes on outside the cell as well as by the cell's genetic program.

An order to make a protein begins when the appropriate genes are "transcribed" from the DNA into strands of another kind of nucleic acid, called messenger ribonucleic acid (mRNA). Messenger RNA is manufactured by transcribing just one chain of the DNA double helix (one side of the twisted ladder). A strand of mRNA is complementary to the DNA from which it is transcribed, except that each adenine of the DNA is paired with a uracil (U), instead of with thymine. For example, a stretch of DNA bases ATCG is transcribed into the mRNA sequence UAGC.

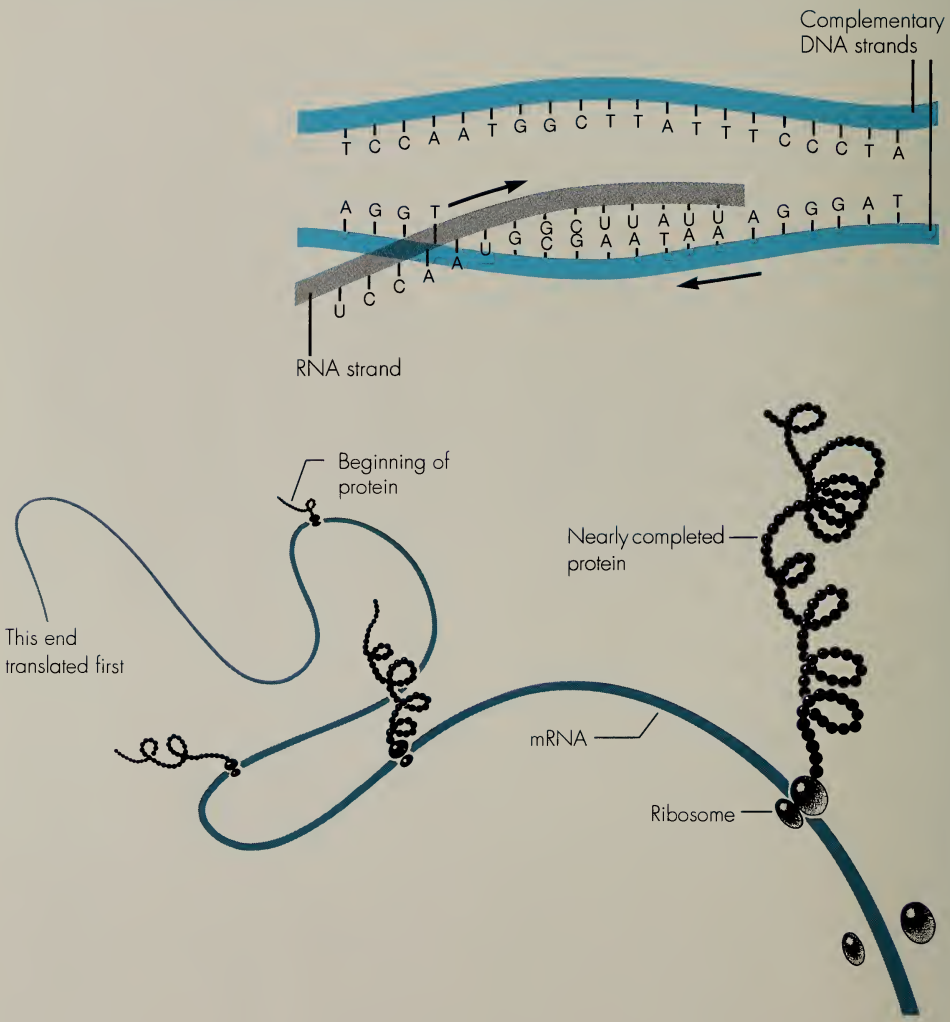
After additional processing, the mRNA carries its message into the cytoplasm, while the DNA remains safely in the nucleus, somewhat like the printing block in a printing press. It may be that the mRNA gets out through "gates" in the nuclear membrane called nuclear pore complexes, although this theory is still unproved.

Once in the cytoplasm, the messenger RNA carries its instructions to tiny organelles called ribosomes, the "factories" in which the next step of protein manufacture, called translation, takes place.

Chromosomes of a normal human male.



In the nucleus, DNA's instructions are transcribed (top) into a messenger molecule of ribonucleic acid (RNA). The code in a strand of messenger RNA is translated into a protein (bottom) in tiny organelles, called ribosomes, in the cytoplasm.



RIBOSOMES, THE "PROTEIN FACTORIES"

Ribosomes, which were discovered in the mid-1950's, are extremely tiny—less than 30 nanometers in diameter. However, due to their crucial role in protein manufacture, ribosomes can also be extremely numerous. In *E. coli*, for example, ribosomes account for one-fourth of the cell's mass. Each ribosome is made of two unequally sized subunits, which are composed of at least 40 different proteins and a form of RNA called ribosomal RNA.

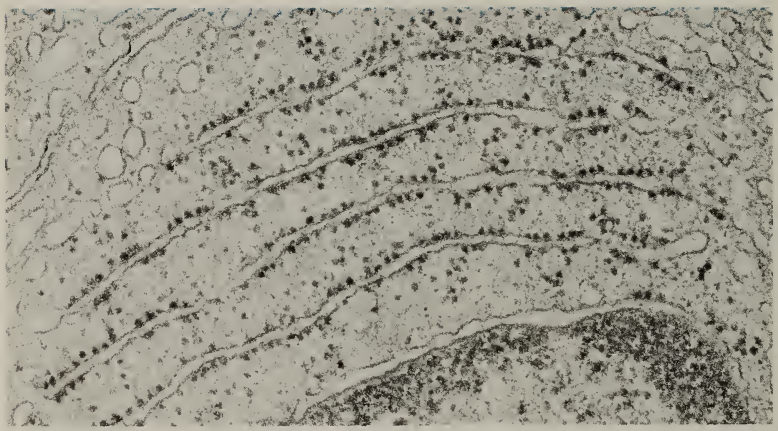
During translation, a strand of mRNA moves between the two parts of a ribosome like a piece of thread being pulled through the eye of a needle. The ribosome "reads" the message of the mRNA not one nucleotide at a time, but rather in groups of three. These groups, called codons, are like words. Each word specifies one of the 20 different amino acids (the chemical subunits that form proteins) or is a signal to start or stop making a protein. For example, the codon AGC in mRNA is translated into the amino acid serine, whereas nucleotides in a different order, say GCA, code for alanine.

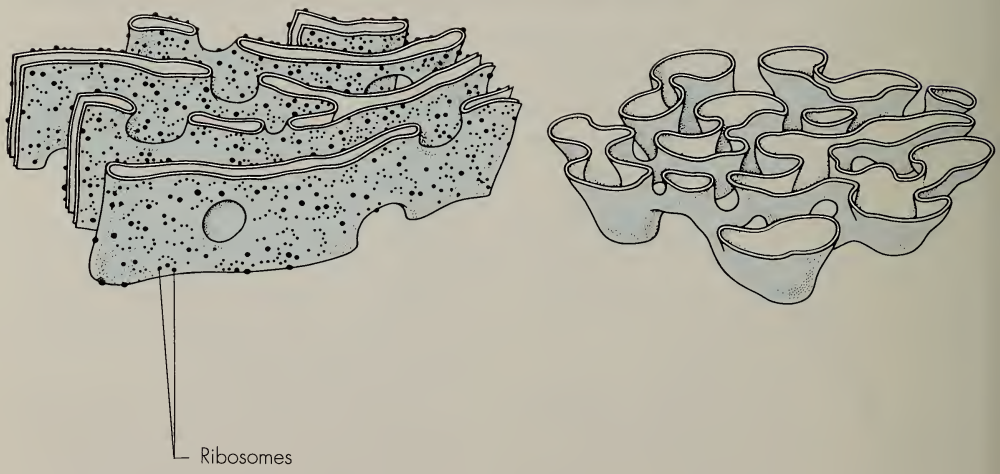
The amino acids called for by the mRNA are brought from the cytoplasm to the ribosome by a third kind of RNA, transfer RNA (tRNA). This small molecule is a connector: one end carries three nucleotides, known as the "anticodon," which will join to a codon in the mRNA according to the rules of base pairing (A with U, and G with C). The molecule's other end carries an amino acid. As the mRNA passes through the ribosome, tRNA brings the correct amino acids in and they are linked together by peptide bonds to form a polypeptide chain. When all the amino acids for a protein are joined, the chain is released.

Each strand of mRNA can be read many thousands of times. Indeed, at any one moment a strand of mRNA containing the transcript for a protein may be attached to 30 separate ribosomes. Moreover, ribosomes work very quickly to connect the required amino acids into a protein. Each ribosome in a single *E. coli*, for example, can link 15 amino acids in a second. The speed and efficiency of translation means that each gene is capable of directing the manufacture of very large quantities of protein. For example, in each cell of a silk worm's silk gland there is a single gene that codes for the protein fibroin, the chief component of silk. Each time it is activated, the gene can make 10,000 copies of its specific mRNA, and *each* copy of mRNA can direct the synthesis of 100,000 molecules of fibroin. In 4 days, a silk gland cell can manufacture a billion molecules of fibroin!

Ribosomes fall into two categories: those that are free in the cytoplasm and those that are bound to membranes. The two kinds of ribosomes play similar roles in the manufacture of proteins. But while the free ribosomes leave the proteins equally free to float in the cytoplasm, the bound ribosomes transfer their finished proteins into a large, cobwebby organelle—the endoplasmic reticulum.

Electron micrograph (top) shows the folds of the endoplasmic reticulum thickly dotted with tiny dark bodies, the ribosomes. Drawings (below) show both the ribosome-covered rough endoplasmic reticulum (left) and the ribosome-free smooth endoplasmic reticulum (right).





THE ENDOPLASMIC RETICULUM

In 1945, as the electron microscope was becoming a useful research tool, Albert Claude of Belgium and Keith Porter, who was then at The Rockefeller Institute, used it to discover a vast network of channels bounded by membranes in the cytoplasm of chick embryo cells. At times this network looked like the concentric circles of a slice of onion. Porter called this network the endoplasmic reticulum because it was more concentrated in the inner (endoplasmic) region of the cell than in the peripheral (ectoplasmic) region. Similar networks were later found in all eukaryotic cells, except mammalian red blood cells.

It was discovered that the membranes of this endoplasmic reticulum all interconnect, forming a system of tubes and flattened sacs that is continuous with the nuclear membrane. In effect, this system divides the cytoplasm into two main regions, one enclosed within the "plumbing" and the other forming the outer region, or cytoplasmic matrix.

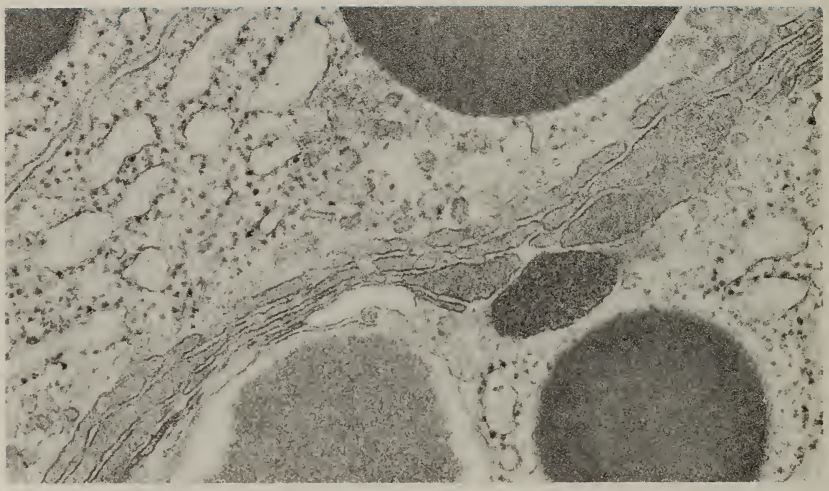
Some parts of this membrane look smooth, while others appear "rough" because they are dotted with ribosomes that form granules on their outer surfaces. These ribosomes deposit newly formed proteins into the lumen, or inner space, of the endoplasmic reticulum. The endoplasmic reticulum then segregates the proteins into those that will be needed in the cytoplasm and those that will be transported to other organelles or secreted from the cell.

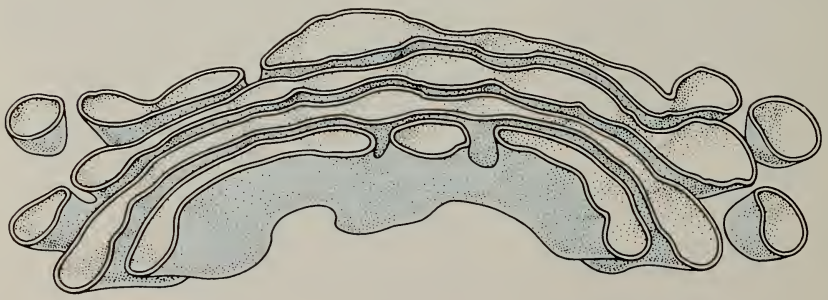
In the mid-1950's, George Palade, then of The Rockefeller Institute, concluded that the amount of rough endoplasmic reticulum in a cell corresponds closely to the quantity of protein the cell exports. Those white blood cells that produce infection-fighting immune system proteins called antibodies have highly developed rough endoplasmic reticula, for example. These antibodies are found mainly in cellular storage areas, from which they go forth to combat infections. The smooth endoplasmic reticulum, on the other hand, is particularly well developed in cells where it takes on some extra function —for example, in liver cells, where it breaks down drugs by making them water soluble.

In addition to its role in protein segregation, the endoplasmic reticulum is the cell's membrane factory. Phospholipids and cholesterol, the main components of membranes throughout the cell, are synthesized in the smooth portion of the endoplasmic reticulum. These compounds form the coating of protein-filled sacs, called vesicles, that "bud off" from the endoplasmic reticulum, migrate to another organelle, fuse with it, and then deposit the protein cargo.

Most of the proteins leaving the endoplasmic reticulum are still not mature; they must undergo further processing in another organelle, the Golgi apparatus, before they are ready to perform their functions within or outside the cell.

Electron micrograph (top) and drawing (bottom) show a layer of cup-shaped sacs making up a Golgi apparatus.





THE GOLGI APPARATUS, FINAL PROTEIN SORTER

In 1898, the Italian scientist Camillo Golgi, who had been studying stained owl and cat nerve cells under his light microscope, saw a cell structure that did not look like the nucleus. Although some biologists at the time thought the structure was just an artifact—perhaps related to the stains Golgi had used—Golgi believed the newly found organelle played a role in protein secretion.

In the 1960's, Palade and his colleagues confirmed Golgi's theory by using radioactive labeling, staining, and electron microscopy to follow proteins in pancreatic cells as they moved from the rough endoplasmic reticulum, through the Golgi apparatus, and into the secretory granules that carried them out of the cell. Although the details are still unclear, it is now known that the Golgi apparatus plays an important role in transforming many newly made proteins into mature, functional ones by "labeling" them with chemical tags and "shipping" them to their destinations.

Each Golgi apparatus consists of a stack of flat, membranous sacs that are piled one on top of the other like dinner plates. The stack is composed of at least three chemically distinct regions, and each sac in the organelle contains enzymes that modify proteins as they pass through. The sacs closest to the nucleus receive vesicles filled with protein molecules from the endoplasmic reticulum. The proteins must pass through all the sacs in sequence to be processed correctly.

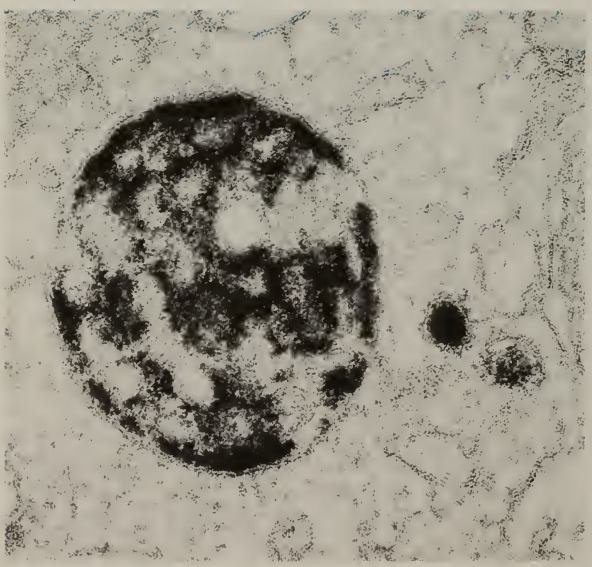
Why does the cell go to such elaborate lengths to modify and sort proteins? According to James Rothman of Princeton University, the compartmental organization of the Golgi apparatus is "crucial to the functioning of the cell, because without it thousands of enzymes would be randomly mixed, resulting in a chaotic splay of biochemical activity." The Golgi apparatus controls the chaos by packaging proteins into vesicles as they pass through the organelle. The protein-filled vesicles then migrate to another organelle or to the cell's surface, where they fuse with the cell's outer membrane and release their contents. This is how cells secrete hormones, enzymes, and other types of proteins as needed.

Inside the Golgi apparatus, proteins are modified depending upon their ultimate destinations. For example, proteins bound for the cell's surface membrane are modified in one way, while proteins that will eventually move to the cell's "digestive" organelles undergo a different series of changes.

LYSOSOMES AND PEROXISOMES, THE CELL'S "DIGESTIVE SYSTEM"

When a white blood cell engulfs a bacterium and destroys it, the white cell's lysosomes do most of the work. They fuse with the vesicle of engulfed material and release digestive enzymes to break up the material. Similarly, when a cell takes in large molecules of food, enzymes in the lysosomes break the food down into smaller and simpler products that the cell can use. These products diffuse through the lysosomes' membranes and go into the rest of the cell, where they serve as building blocks for various structures, until nothing is left inside the lysosomes but indigestible material and the lysosomes become what are called residual bodies. In some cells, the residual bodies then migrate to the cell surface and eject the undigested material into the external environment.

Lysosomes were discovered by a Belgian researcher, Christian de Duve, in 1949, when he homogenized some animal cells and separated them into various components by running them through an ultracentrifuge. After one of these components had been left standing for a few days, de Duve noticed that the level of a certain enzyme in it rose dramatically. Since this enzyme had not attacked any part of the cells before they were ground up, he reasoned that it must have been kept segregated within the cell—probably inside some kind of organelle. He also knew that he had used a relatively gentle method of homogenization, which could have allowed



An electron micrograph showing two small lysosomes and one large lysosome. These organelles contain enzymes capable of breaking down various substances.

the unknown organelle to remain intact. Presumably, it released its contents later.

De Duve's biochemical approach, for which he shared the Nobel Prize with Claude and Palade in 1974, was soon supplemented by electron microscopy. But it proved difficult to identify the new particles, since, unlike other organelles, lysosomes vary in shape from cell to cell. Finally, in 1955, Alex Novikoff of the Albert Einstein College of Medicine clearly identified some lysosomes in rat liver cells, and it is now known that lysosomes (whose name refers to the fact that their enzymes can lyse, or digest, substances) exist in all eukaryotic cells.

At about the same time that de Duve and his colleagues were describing the biochemistry of lysosomes, they detected another enzyme-containing organelle. In 1965, de Duve proposed that the organelle be called a peroxisome because it appeared to both generate and break down hydrogen peroxide, a corrosive molecule composed of two atoms each of hydrogen and oxygen.

Today it is known that peroxisomes exist in most eukaryotic cells, and that they are especially prominent in mammalian liver cells. The membrane that surrounds a peroxisome is unusually permeable, permitting many small molecules to enter easily. Peroxisomal enzymes remove hydrogen atoms from these small molecules and join the hydrogen to atoms of oxygen to form hydrogen peroxide. One of the peroxisomal enzymes, catalase, then neutralizes the hydrogen peroxide by breaking it down into water and oxygen. This two-step process is the method that peroxisomes in the liver use to break down molecules of alcohol into substances that can be eliminated from the body. About one-quarter of the alcohol that enters the liver is processed in peroxisomes.

In his early descriptions of peroxisomes, de Duve called them "fossil organelles" because of their primitive nature and seemingly expendable actions. (All of the enzymes found in peroxisomes are also found elsewhere in the cell.) However, it is now known that a rare, fatal genetic disorder called Zellweger's syndrome is the result of malformed peroxisomes, indicating that peroxisomes do have a vital role in the healthy cell.

The ability of peroxisomes to use oxygen in chemical reactions has led many scientists to conjecture that these organelles represent a relic of an attempt by the precursors of eukaryotic cells to "cope" with oxygen as it accumulated in the prehistoric atmosphere. Peroxisomes cannot, however, couple oxygen use with energy production. That ability is restricted to chloroplasts and mitochondria—the "energy converters" of eukaryotic cells.

Lysosomes in Health and Disease

Lysosomes are known to contain over 40 different enyzmes that can digest almost anything in the cell, including proteins, RNA, DNA, and carbohydrates. These enzymes work best in environments more acidic than that found in the cytoplasm, and lysosomes are specially equipped to provide this acidic environment. As corrosive as these enzymes are, they do not ordinarily damage the cell because the lysosomal membrane remains intact.

When cells are programmed to die in some normal process of embryonic development, however—for example, in the metamorphosis of insects—the lysosomes' membranes become permeable and release their enzymes to digest the cells from within. In very old cells, too, the lysosomes may release their contents, which destroy the cell. A more limited form of "autodigestion" can also occur in cells that have been injured by lack of oxygen, an excess of vitamin A, exposure to certain cancer-causing agents, or starvation. In these situations, lysosomes break down a portion of the cell's contents, liberating amino acids that can be used to make the most essential substances and ensuring the cell's survival without major damage.

Lysosomal membranes prevent enzymes from leaving the organelle, but permit entry of new enzymes if they have been properly labeled in the Golgi apparatus. However, if a lysosomal enzyme is not produced or if an enzyme is not properly "addressed" in the Golgi, a lysosomal storage disease can result. Persons with the lysosomal storage disease known as Hurler's syndrome, for example, cannot break down large molecules of sugar-fat compounds called glycosaminoglycans because their lysosomes do not contain the enzyme iduronidase. Glycosaminoglycans accumulate in the lysosomes, swelling them so much that the functioning of the entire cell is impaired.

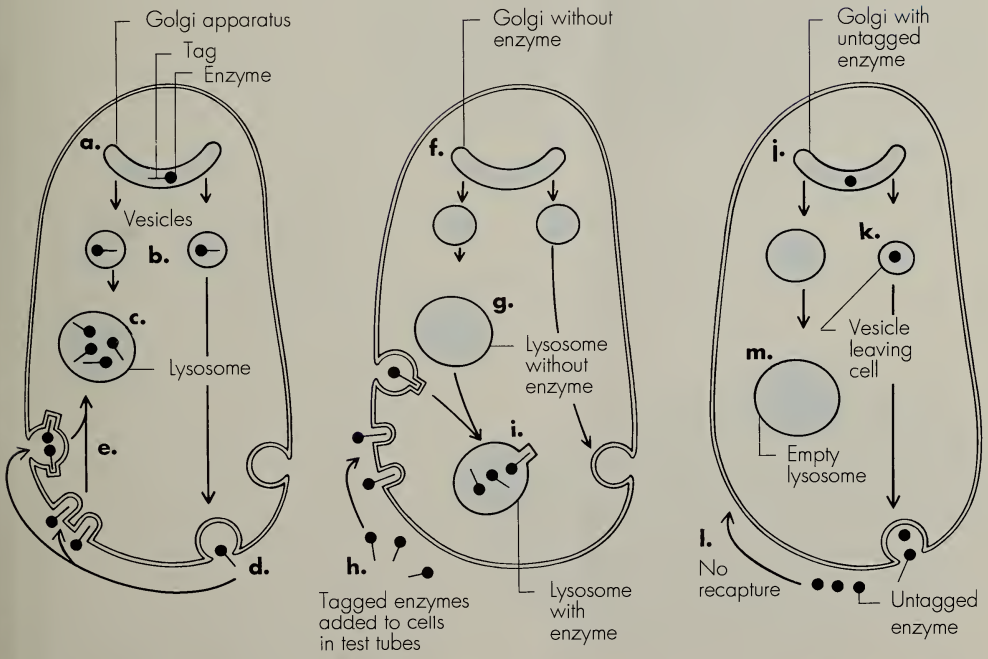
A particularly severe lysosomal disorder is known as I-cell disease. Children born with this disease lack the entire range of lysosomal enzymes; the enzymes are made, but they are dumped outside the cell instead of being sent to the lysosomes. Various cellular nutrients thus cannot be digested and so pile up in dark lumps, called inclusion bodies, within the lysosomes. The disease affects the kidneys, heart, and nervous system, and children with it usually die of heart failure or pneumonia before reaching puberty.

In the early 1970's, Elizabeth Neufeld, who was then at NIH, showed that the lysosomal enzymes of persons with I-cell disease emerge from the Golgi apparatus without the chemical tag they need to be directed to the lysosomes. She also showed that the defect could be corrected in test-tube cultures of cells taken from people with the disease. The corrective factors she supplied were the specific, properly tagged enzymes that the cells lacked.

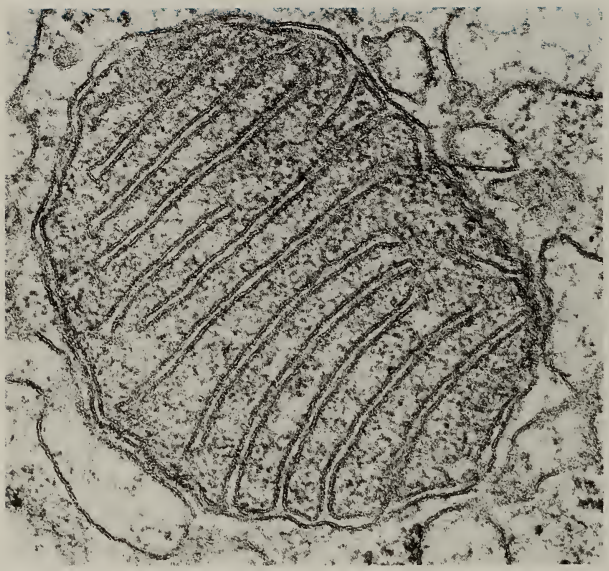
Scientists hoped that such "enzyme replacement therapy" could be used to treat people with enzyme disorders. To date, however, it has proved difficult to deliver the missing enzymes to the cells that need them and to induce the lysosomes in each cell to take up the enzymes. When purified enzymes are injected directly into the body, they tend to be quickly destroyed or inactivated. It is particularly difficult to get enzymes into the brain—an important problem now under investigation, since several lysosomal diseases produce severe mental retardation.

In many ways, then, health and disease depend on the lysosomal membrane's ability to control the uptake and release of its contents. Some substances seem to stabilize and strengthen the membranous envelope, while others weaken it. In the future researchers may find ways to use these properties for the prevention of disease or for therapy.

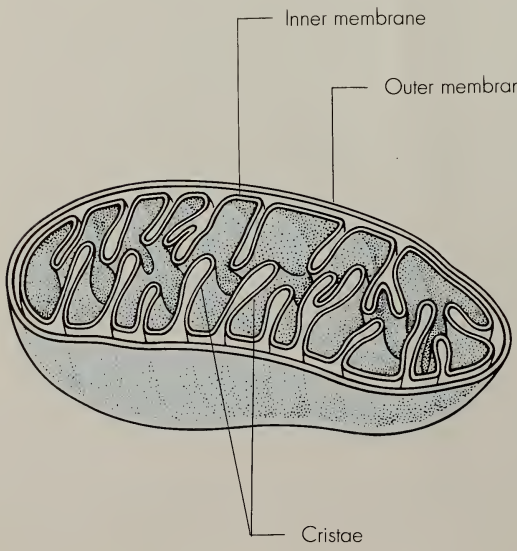
The sorting of lysosomal enzymes in a normal cell is shown on the left. First, enzymes receive a chemical "address label" in the Golgi apparatus (a), and move in vesicles (b) to a lysosome (c). Any enzyme that is accidentally swept out of the cell (d) is recaptured and taken back to the lysosome (e). If some part of this process goes awry, a lysosomal storage disorder can result. For example, in Hurler's syndrome (center), an enzyme is not produced (f), and the lysosome therefore lacks that enzyme (g). If correctly tagged enzyme is added to the cells in test tubes (h), the cells can capture the enzyme and take it to the lysosome (i). In I-cell disease (right), enzymes are correctly made, but they are not tagged in the Golgi (j), and therefore are not sent to the lysosome. When such enzymes leave the cell (k), they cannot be recaptured (l) and so the lysosome remains empty (m).



Normal cell **Hurler's syndrome** **I-cell disease**



Electron micrograph showing one of the cell's many mitochondria, the organelles that convert energy from food into a form that can be stored.



A mitochondrion is shown as if it had been sliced longitudinally. The inward folds of the inner membrane are called cristae.

MITOCHONDRIA, ENERGY CONVERTERS IN THE CELL

One and a half billion years ago, scientists believe, cells derived the energy they needed through a variety of relatively inefficient processes, none of which required oxygen. Oxygen, a waste product of some of these processes, gradually began to accumulate in the atmosphere. It was at this time, scientists hypothesize, that a pre-eukaryotic cell engulfed another primitive cell that had somehow acquired the ability to use oxygen to produce large quantities of energy. Over the eons, a symbiotic relationship evolved between the cells, and today all plant and animal cells have organelles that are the descendants of the primordial energy producers. In animal cells, these organelles are called mitochondria, while the energy-producing organelles in green plants are called chloroplasts.

Chloroplasts use the energy in sunlight to convert molecules of carbon dioxide and water into molecules of sugar, a form of energy that can be stored in the plant cell. (Molecular oxygen is given off as a byproduct of this process, which is called photosynthesis.) When an animal eats a plant (or another animal that has itself eaten plants), the plant's sugars are broken back down into carbon dioxide and water, with the help of oxygen and an arsenal of enzymes, releasing large amounts of stored energy. This energy is immediately converted to yet another form—molecules of adenosine triphosphate (ATP).

ATP is often called the universal currency of cellular energy. It is a convenient way for cells to store the energy they need for such processes as protein manufacture, DNA replication, and the construction of new organelles. ATP is also required for such mechanical work as muscle contraction, pumping water through membranes, and cell movement. Except for the first stage of sugar breakdown, the entire, complicated process of energy transfer from sugar to ATP takes place within the animal cell's mitochondria. (Plants also have mitochondria, although they make most of the ATP they need within their chloroplasts.)

Besides supplying energy, mitochondria apparently help to control the concentration of water, calcium, and other charged particles (ions) in the cytoplasm. They also break down and recycle the energy contained in fatty acids and amino acids.

Mitochondria are the largest organelles in an animal cell, after the nucleus, yet some cells have more than a thousand of them. They vary in diameter from 0.5 to 1 micrometer and in length up to 7 micrometers, and can be seen with a good light microscope. Mitochondria are usually represented as oval shaped, but in life they can change shape quite readily. They swell or contract in response to various hormones and drugs and during ATP manufacture. This swelling and contracting appears related to the movement of water through cells, and is particularly

evident in the kidneys, through which 180 liters of water are filtered daily.

Although mitochondria were first observed in the 1880's, it took many years for scientists to understand the organelles' function. The process by which mitochondria use oxygen to release the chemical energy stored in food is called cellular respiration. Early in this century, it was discovered that the biochemical reactions of respiration fall into two main groups: the carbon pathway, in which sugar is broken down into carbon dioxide and hydrogen; and the hydrogen pathway, which transfers hydrogen to oxygen in stages, forming water and releasing energy.

In the hydrogen pathway, the hydrogen's electrons pass through an "electron transport chain" made up of enzymes. As they move from enzyme to enzyme, the electrons give up part of their energy. This energy is then stored in molecules of ATP. In the end, 38 molecules of ATP are formed for every molecule of sugar that is used up in respiration.

Mitochondria are marvelously efficient at converting the chemical energy of sugar into ATP. Whereas a man-made engine would be considered very efficient if it converted 25 percent of the energy available in gasoline into mechanical work, mitochondria routinely turn 54 percent of the available energy in sugar into ATP. This efficiency is achieved, in large part, because of the mitochondria's internal structure. In the early 1950's, Palade and a Swedish scientist, Fritiöf Sjostrand, reported that mitochondria are bounded by a membrane and that they have a system of parallel, regularly spaced inner ridges that the scientists named cristae. It is now known that there are two membranes around a mitochondrion: an outer membrane, separated from the rest of the organelle by a fluid-filled gap; and an inner membrane that is folded inward at various points to increase its surface, forming the cristae. This ridged surface allows the enzymes of the electron transport chain, which are attached to the cristae, to be packed more densely within each mitochondrion, thus increasing the organelle's efficiency. This general design seems to have existed unchanged from the time that mitochondria-like cells were free-living organisms.

Mitochondria have also kept other vestiges of their existence as independent organisms. For example, mitochondria "reproduce" by splitting in half as many modern bacteria do; they are not formed by budding from existing cellular structures or built up from simple cellular constituents, as is the case for ribosomes.

More significantly, after a billion or so years of residence within "host" cells, mitochondria (and chloroplasts) still retain some of their own DNA. The amount of this non-nuclear DNA varies significantly from organism to organism. The chloroplasts of plants, for example, have five times more DNA than do the mitochondria of

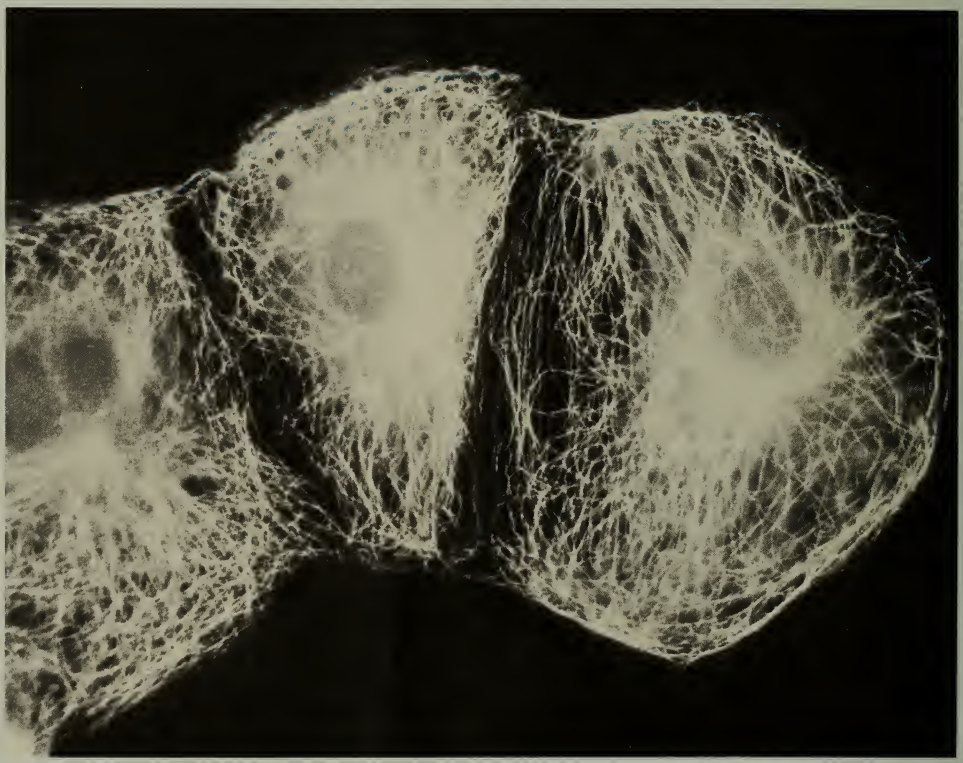
mammalian cells. Human mitochondrial DNA is a closed, circular molecule 16,569 nucleotide pairs long. Although this is less than 1 percent of the total DNA in a human cell, each mitochondrion has enough to code for several of the key inner membrane proteins. (All of the other proteins in a mitochondrion are coded for in the nucleus, made on free ribosomes in the cytoplasm, and imported into the organelle.)

Another curious characteristic of human mitochondria is the fact that all of a person's mitochondria are descendants of those of his or her mother; no paternal mitochondria are present. This fact has proved useful to evolutionary biologists, who can study the passage of mitochondrial DNA from generation to generation while ignoring the "interfering" information contained in the nuclear DNA, which records the genetic contributions of both parents.

Scientists have long suspected that defects in mitochondrial genes could lead to inherited disease in the same way that mistakes in nuclear DNA do. This hunch was not proven until 1988, when Douglas Wallace of Emory University showed that a rare eye disease called Leber's hereditary optic neuropathy is caused by a mutation in mitochondrial DNA. The defective mitochondrial gene prevents the optic nerves from producing enough ATP, and the nerves, which need huge amounts of ATP and are thus particularly sensitive to any deprivation, die. When he announced these findings, Wallace said, "we feel that these alterations [in mitochondrial DNA] may be responsible for a wide spectrum of diseases in the brain, the central nervous system, and the musculoskeletal system."

Mitochondria, chloroplasts, and the other organelles described thus far are surrounded by membranes. But cells can also contain threadlike organelles that lack membranes. These extremely fine structures serve as buttresses, highways, and motile mechanisms for the cell.

These cells have been stained with modified antibodies that attach to the cell's "scaffolding," called the cytoskeleton, and that glow under ultraviolet light.



THE CYTOSKELETON, THE CELL'S PHYSICAL PROPS

Many cells in a multicellular organism must combine the seemingly contradictory traits of stability and mobility. With few exceptions, multicellular organisms begin to develop when a motile sperm meets an egg. Many cell divisions occur, and then cells migrate to their final positions. During life, individual cells divide frequently, and certain specialized cells move through the body to accomplish various tasks. In addition, every cell must have a mechanism for moving materials within itself. Balancing the need for movement is the requirement for cell stability. A cell must maintain its shape against the pressure of surrounding cells. Keeping a cell firm while enabling it to move are the twin roles played by the cytoskeleton.

For a long time, microscopists believed that the cytoplasm surrounding the cell's organelles was completely unstructured. But as scientists began to use newer and gentler fixatives to prepare cells for electron microscopy, a lacy network of fibers was revealed. These structures crisscross the cell like girders and it was hypothesized (and later shown experimentally) that, like an animal's bony skeleton, these structures play a role in giving the cell its shape. For this reason, they are known collectively as the cytoskeleton.

There are three main kinds of cytoskeletal fibers—microfilaments, microtubules, and intermediate filaments—which are distinguishable both by their structure and by their protein composition. All three support and stiffen the cell. In addition to their structural roles, microtubules and microfilaments are essential for a variety of dynamic whole-cell activities, including division, contraction, and crawling, as well as for the movement of vesicles within the cell.

Microfilaments are more commonly called actin filaments because they are composed of "beads" of the protein actin arranged into long, slender chains. Each filament is only 6 nanometers in diameter; they are the finest of the cytoskeletal components. The role that actin filaments play in muscle contraction has been thoroughly studied over the past 30 years. In the 1950's, a British scientist, Hugh Huxley, proposed a model for muscle contraction that has since been shown to be correct. According to the model, each muscle cell comprises parallel rows of actin filaments that alternate with rows of another protein, myosin. When stimulated by an influx of calcium, projecting "arms" of myosin "grab" the adjacent actin filaments and pull, causing the muscle cell to shorten. Contraction is an ATP-requiring process; each "grab" and release uses up one molecule of ATP. In recent years, researchers have found evidence of similar actin-myosin interactions in many other kinds of cells, including cells that secrete hormones and white blood cells that move through the body to fight invading organisms.

Microtubules, at 22 nanometers in diameter, are the thickest of the cytoskeletal components. They were

noticed in the mid-1950's, but were seen only rarely until 1963, when the gentle fixative glutaraldehyde was developed. Each hollow tubule is composed chiefly of small, spherical subunits of proteins called tubulins. Microtubules assemble spontaneously from "pools" of tubulin when needed and, under appropriate conditions, dissolve, or depolymerize, back into their tubulin subunits. (Microfilaments also form and break down spontaneously.) Under the microscope, microtubules can be observed growing and shrinking rapidly. Because microtubules perform so many important functions within the cell, scientists are eager to learn the details of their dynamics.

One of the most vital functions of microtubules is to aid in cell division. Just before a cell divides, small bodies called centrioles (which are themselves composed of microtubules) migrate to the cell's poles. A spindle made of microtubules forms between the centrioles. Chromosomes attach to the spindle, which then helps to guide them to the daughter cells. In 1988, Marc Kirschner and his colleagues at the University of California, San Francisco, found strong evidence that chromosomes move toward the poles as the microtubules slowly dissolve. This indicates that, contrary to what many researchers had assumed, microtubule depolymerization and subsequent chromosome movement apparently do not require ATP.

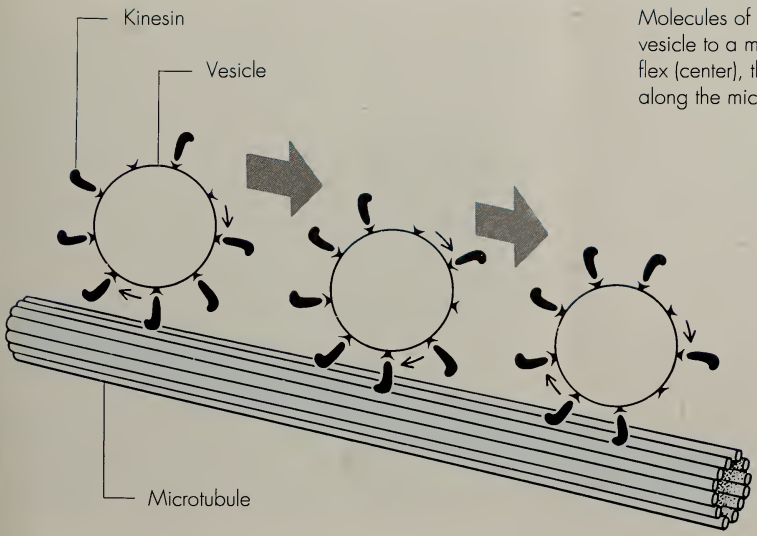
The spindle is easily disrupted by a number of chemicals. Colchicine, an extract of meadow saffron used

The microfilament bundles in this skin cell have been stained with modified antibodies that glow under ultraviolet light.

since ancient Egyptian times as a treatment for gout, stops spindle formation and arrests cell division. In 1967, Edwin Taylor and his associates at the University of Chicago discovered that colchicine did its work by binding to tubulin. Two other chemicals, vinblastine and vincristine, also disrupt spindles and are used as anticancer drugs since they preferentially inhibit the spindles of rapidly dividing cancer cells.

Between cell divisions, microtubules act as miniature highways along which vesicles carrying such materials as hormones, neurotransmitters, and nutrients move. Using new techniques, such as video-enhanced light microscopy, scientists in several laboratories have observed microtubules interacting with a globular protein called kinesin that functions as a molecular motor to move vesicles and organelles along microtubule tracks toward the cell surface. Kinesin also moves vesicles filled with neurotransmitters along the microtubules within nerve cell axons. A motor protein that moves vesicles in the opposite direction, toward the cell's interior, was discovered in 1987.

Microtubules are also involved in the movement of cilia and flagella. These whiplike filaments project from certain cells and perform a variety of tasks. Large numbers of cilia are found on cells that line the respiratory system, for instance, where they help to sweep out dust and debris. Both cilia and flagella play an important role in human reproduction. The coordinated beating of cilia in the



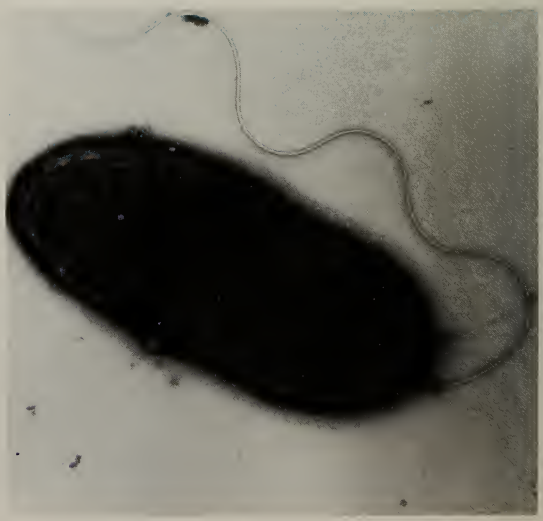
Molecules of kinesin connect a vesicle to a microtubule (left) and flex (center), thus pulling the vesicle along the microtubule (right).

oviduct produces a sort of current that draws the egg into the uterus, while the rapidly thrashing flagella of sperm help them to "swim" toward the egg.

The inherent ability of microtubules and microfilaments to assemble and disassemble rapidly allows for the construction and destruction of these cytoskeletal components to suit the needs of a moving cell. In contrast, intermediate filaments are the most stable of the cytoskeletal fibers. At 8 to 10 nanometers in diameter, they are intermediate in size between microfilaments and microtubules. Intermediate filaments appear in many types of cells, and their precise protein composition depends upon their location. They are prominent in parts of the cell that are under mechanical stress, such as the long axons of nerve cells and the surface of skin cells.

Some researchers have reported that a number of diseases, including Alzheimer's disease and Parkinson's disease, are associated with changes in the intermediate filament arrays in cells. However, while intermediate filaments obviously have important functions in cell physiology, very little is now known about the cause or effect of their alteration during disease.

Nevertheless, an understanding of intermediate filaments is proving valuable in tumor diagnosis. If cancerous cells arise in one organ and then migrate to another, a clinician can study the intermediate filament composition of the tumor cells to



Some microorganisms are equipped with a flagellum (composed of microtubules), which thrashes to propel the animal.

determine the cancer's origin. This knowledge helps physicians decide on the best course of treatment for that particular tumor.

Some scientists believe that intermediate filaments may play a role in carrying certain messages from the cell's surface to the nucleus, where they turn genes on. Research is under way to discover if this is, in fact, the case.

Current investigations of the cell's organelles—the nucleus, ribosomes, endoplasmic reticulum, Golgi, lysosomes, peroxisomes, mitochondria, and cytoskeleton—hold great promise for the solution of problems of basic biology and clinical medicine. However, the key that may unlock the greatest number of health benefits may well be found in the cell's filmy membranes, particularly the surface membrane, which plays a pivotal role in maintaining the integrity of the cell and, in a larger way, in protecting the health of the organism.

THE SURFACE MEMBRANE, VERSATILE GATEKEEPER

"In the beginning," writes Gerald Weissmann of New York University, "there must have been a membrane! Whatever flash of lightning there was that organized purines, pyrimidines, and amino acids into macromolecules capable of reproducing themselves, it would not have yielded cells but for the organizational trick afforded by the design of a membrane wrapping." Weissmann imagines these primitive membranes forming bubbles in which the first macromolecules were enclosed and protected from dissipation in the salty primordial seas.

A cell's outer membrane is often thought of as a boundary that defines the living cell from its surroundings. And, indeed, surface membranes are crucial in keeping cells intact. Moreover, the internal membranes that wrap around many organelles in eukaryotic cells separate the cytoplasm into discrete regions, somewhat like the walls that form rooms in a house. These inner membranes enable the cell to perform many biochemical activities simultaneously, thereby greatly increasing the cell's efficiency.

Yet despite its barrier functions, the cell membrane—which is often less than 0.01 micrometer thick—is not impassive. Rather, it is exquisitely sensitive to its surroundings and selectively allows certain substances to enter and leave the cell while barring others. It takes in nutrients and excretes wastes. It sends and receives chemical and electrical messages, including signals for the cell to manufacture proteins or to divide. In multicellular organisms, it joins with other cells to form tissues.

These myriad abilities are due to the membrane's composition. Although surface membranes differ in their precise composition depending on the cell's type, and although a membrane's configuration changes from moment to moment, all membranes are composed of two basic kinds of molecules—proteins and lipids (fats).

In 1972, S. Jonathan Singer and Garth Nicolson of the University of California, San Diego, proposed a model to describe the relationship of proteins and lipids in an idealized membrane. They compared the proteins to "icebergs floating in a sea of lipids," and suggested that some of the proteins are folded so that the "tips" poke above and below the plane of the membrane, while the middle of the protein is embedded in the membrane itself.

Although such tripartite proteins were unknown at the time Singer and Nicolson proposed their model, they have since been shown to exist. Many other membrane proteins that are attached either to the inner or outer face of the surface membrane have also been studied in detail in the years since Singer and Nicolson proposed their so-called fluid-mosaic model. It is now known that the proteins do not float through the lipids unrestrained. Rather, they are tethered in a general region by slender

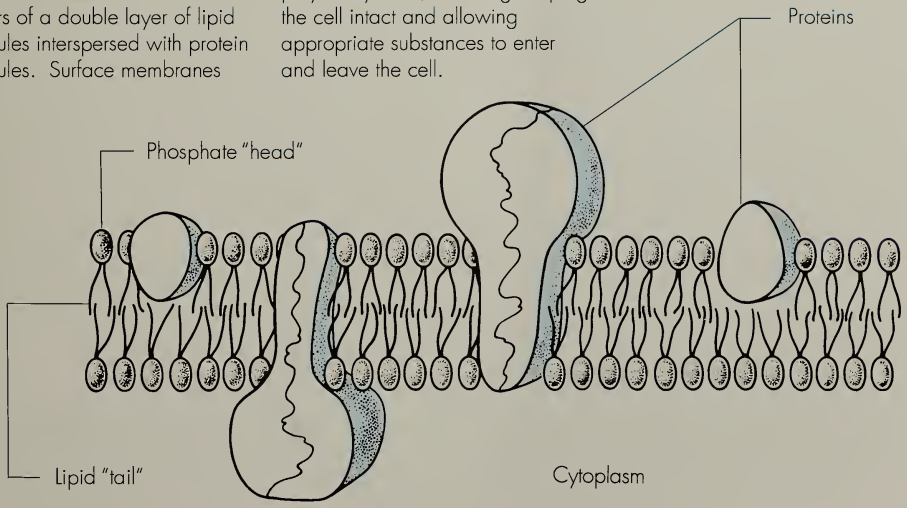
fibers somewhat like hot-air balloons are tethered by guy wires before liftoff.

The lipids that make up the bulk of a cell's surface membrane fall into three classes: phospholipids, steroids (primarily cholesterol), and glycolipids. About half of the molecules in an average membrane are phospholipids. Each phospholipid molecule has a water-seeking (or hydrophilic) phosphate "head" and two flexible, water-avoiding (or hydrophobic) lipid "tails." In a surface membrane, phospholipids spontaneously arrange themselves into a bilayer (double layer) with phosphate heads touching the watery interior and exterior of the cell, and lipid tails buried in the middle of the layer.

Cholesterol is abundant in many animal cell membranes; sometimes there is as much as one cholesterol molecule for every phospholipid. Cholesterol is a rigid molecule that gives the surface membrane strength. It is manufactured within the cell (on the endoplasmic reticulum) and is also brought into the cell from the blood. Cholesterol is present only in animal cells; plant cells are stiffened by a very rigid cell wall composed mainly of cellulose.

Glycolipids are composed of a sugar ("glyco" is derived from the Greek word for sweet) and a lipid portion, and make up about 5 percent of the lipid population. A person's blood group (O, A, B, or AB) is determined by the particular kind of glycolipids present on the surface of his or her red blood cells.

The surface membrane of a cell consists of a double layer of lipid molecules interspersed with protein molecules. Surface membranes play many roles, including keeping the cell intact and allowing appropriate substances to enter and leave the cell.



Liposomes—Drug Delivery Vehicles of the Future

Can microscopic artificial membranes help doctors treat cancer, angina, and viral infections more effectively, and lead to better vaccines, bronchodilators, eye drops, and sunscreens? The researchers who are developing liposome technology hope so. A liposome is a tiny sphere of fatty molecules surrounding a watery interior. Because they are made of the same material as cell surface membranes, liposomes stick to cells and are not toxic. These characteristics make them attractive candidates for drug delivery vehicles.

In 1980, two groups of researchers used liposomes filled with a common antibiotic to cure mice having a severe, but localized, infection. The infected cells were of a kind that is specialized to take up foreign bodies, and so they readily engulfed the liposomes. However, getting other kinds of cells to take up drug-filled liposomes has proven to be more difficult. A number of groups of researchers are experimenting with antibody-tagged liposomes filled with an anticancer drug. The liposomes are guided to the diseased tissue by the antibodies, which seek out cancerous cells but spare healthy ones. This selectivity allows smaller amounts of a drug to be used with greater effect, an important advantage considering the serious toxicity of many anticancer drugs.

Other research teams are developing liposome-drug compounds that would be injected into muscle to release growth hormone or anticancer agents over a period of weeks. Scientists also hope to use liposomes to improve the safety and effectiveness of vaccines, including an influenza vaccine. As the cost of both natural lipids (extracted from egg yolk and soybeans) and artificial lipids declines, the future may bring many other liposome-containing medical products as well as nonmedical items, such as cosmetics.

DIRECTING TRAFFIC ACROSS THE SURFACE MEMBRANE

The oily lipids of a cell's surface membrane serve admirably to prevent the cell's water-based contents from leaking out. However, in "solving" this problem, the cell is confronted with another—how to transport wastes and cell products out of the cell and allow nutrients and other substances in, without either shrinking or swelling too much.

Over eons, cells have evolved a wide variety of transport mechanisms to ferry substances across the hydrophobic barrier. Transport may be either "passive," which requires no energy, or "active," which uses ATP. Also, a molecule may either pass directly through the lipid layer or it may be carried in by a surface protein in a process called receptor-mediated endocytosis. (Endocytosis can also occur without the involvement of a surface protein. In both styles of endocytosis, a bit of the surface membrane folds inward around the entering particle, then pinches off and carries the particle into the cell. The opposite process, exocytosis, occurs when vesicles moving from the cell's interior fuse with the surface membrane and spill their contents outside of the cell.) The method used to import or export substances depends on a combination of the transported item's size, chemical composition, electrical charge, and abundance (concentration), as well as on its ability to dissolve in lipids.

Oxygen, nitrogen, and other small molecules that can dissolve easily in lipids move readily back and forth across the bilayer. Importantly, because of its small size and the distribution of its electrical charge, a water molecule can also pass relatively easily through the membrane even though water is quite insoluble in oil.

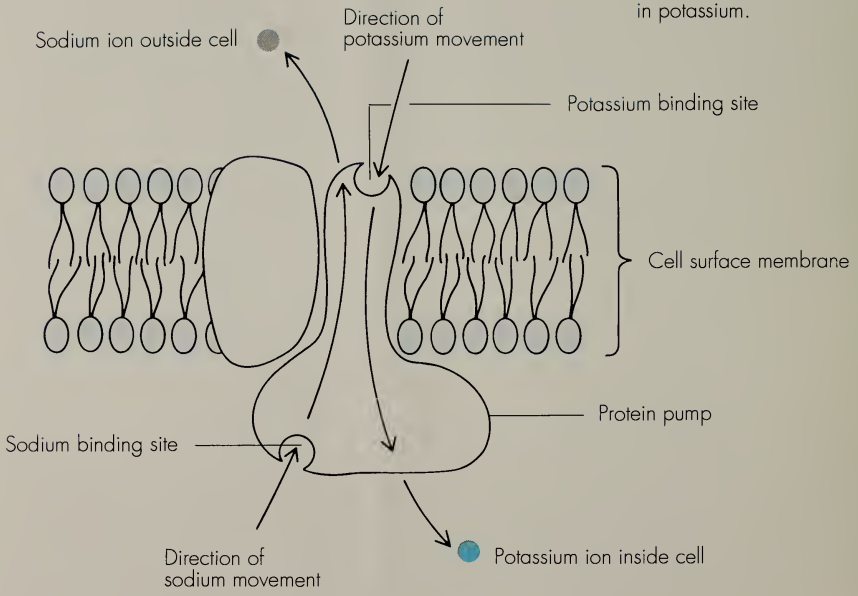
In contrast, large molecules, such as proteins and sugars, cannot pass through the lipid bilayer. A variety of transport systems, many of which involve surface proteins, are used to ferry these substances into and out of the cell. Surface membrane lipids are also highly impermeable to all ions, no matter how small they are. ATP-requiring protein "pumps" are employed to transport ions.

One well-studied pump system is the sodium-potassium pump. This membrane protein consumes more than a third of the cell's total ATP production in an endless cycle of pumping sodium ions out of the cell while drawing potassium ions in. This frantic work results in an "ion gradient" in which there is a high concentration of sodium ions outside the cell and a high concentration of potassium ions inside. This creates a source of potential energy analogous to the potential energy created when water is held behind a dam. If the dam is lowered, water will flow over it and can be used to turn turbines or do other work. In the same way, if the membrane pumps momentarily permit an inward flux of sodium ions (accompanied by an outward rush of potassium ions), a variety of tasks,

including the propagation of electrical signals among nerve cells, can be performed.

Another very important function of the sodium-potassium pump is to keep the total number of ions on both sides of the membrane approximately equal, thereby preventing the cell from swelling or shrinking. Ouabain, a crystalline substance derived from the seeds of an African shrub, disrupts the sodium-potassium pump and causes cells to swell and burst. African hunters use it in large amounts to make poisoned darts, and doctors sometimes prescribe it in small amounts as a heart stimulant.

This schematic drawing shows how the sodium-potassium ion protein pump in the cell's membrane forces sodium out of the cell, while pulling in potassium.



SELECTIVE IMPORT, THE JOB OF RECEPTOR PROTEINS

Animal cells are surrounded by blood that contains many vital substances, some of which are present only in minute quantities. From this rich blend of ingredients, each cell must extract only those things it needs, and reject anything it is not equipped to handle. Such selective import is performed by specialized surface membrane proteins that are collectively called receptors. The unique characteristics of a cell depend, in large measure, on what kinds of receptors it has. Like a lock that accepts only an appropriately shaped key, each different receptor will function only when the correctly shaped blood-borne molecule (called a ligand) attaches to it.

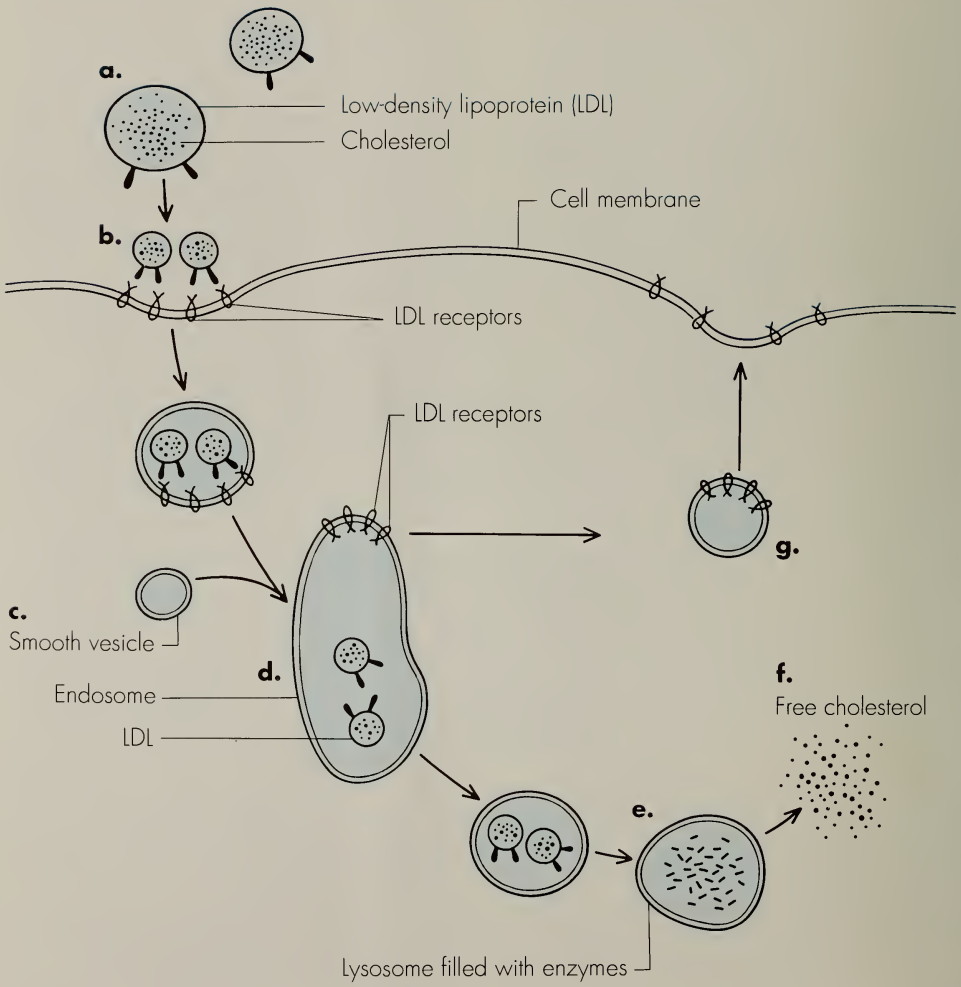
One important receptor is the LDL (low-density lipoprotein) receptor, which admits cholesterol into the cell. When a normal cell needs more cholesterol than it has produced, it synthesizes more LDL receptors. The liver manufactures cholesterol and releases it into the blood, and it is carried by LDL's to the waiting LDL receptors. When the LDL's enter the cell, lysosomes break them down and release the cholesterol. As soon as the cholesterol in the cytoplasm reaches a certain concentration, the cell stops making new LDL receptors.

LDL receptors bound to LDL's do not enter the cell one at a time. Rather, the complexes are rounded up and migrate to a place on the membrane where the surface begins to sink inward. These places, called coated pits, eventually pinch off and move into the cell. During this process, bits of the surface membrane are brought into the cell along with the LDL complexes. However, the cell does not become smaller, because the "lost" membrane is replaced by vesicles moving outward from the cell's interior. It has been calculated that an area of membrane the size of the entire cell surface is recycled in this way every 50 minutes.

Not all of the molecules that influence cell function are absorbed by the cell. Many hormones, for instance, exert their effects in an indirect manner, through receptor proteins that transduce the signal and generate "second messengers" within the cell. One of the best understood of these second messenger systems employs proteins called G proteins because they add phosphate atoms to a substance that contains guanine.

In the G protein system, when a "first messenger" (such as a hormone) reaches the cell surface, it binds to a receptor that then sends a signal to a G protein located on the cytoplasmic side of the cell membrane. Depending on its type, the activated G protein then either stimulates or inhibits the activity of any of a number of enzymes, including one called adenylate cyclase. This enzyme causes cyclic AMP, a common second messenger, to be produced. Cyclic AMP then sets off a chain reaction that eventually results in changes in the shapes of certain proteins in the cell, which, in turn, lead to still other cellular responses. One of these

Steps in the endocytosis of cholesterol. Low-density lipoproteins (LDL's) filled with cholesterol approach the cell (a) and attach to LDL receptors in the cell's surface membrane (b). After passing into the cell, a vesicle filled with LDL's joins with a smooth vesicle (c) to become an endosome (d), in which the LDL's and the LDL receptors pull apart. A vesicle filled with LDL's migrates to a lysosome (e), which breaks down the LDL's and releases free cholesterol into the cytoplasm (f). Meanwhile, the LDL receptors are returned to the cell surface (g).

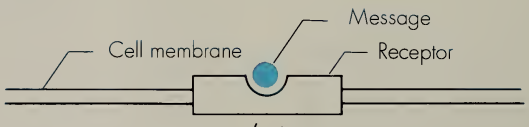
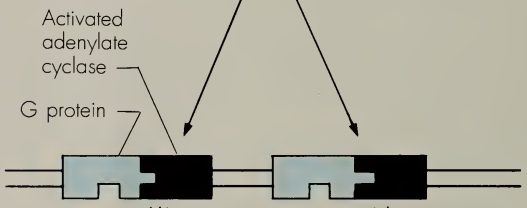
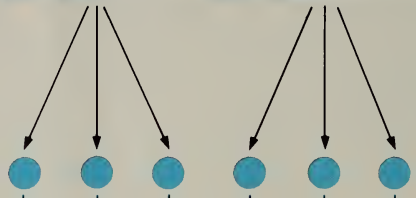
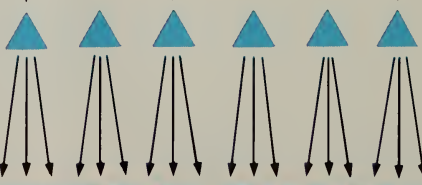
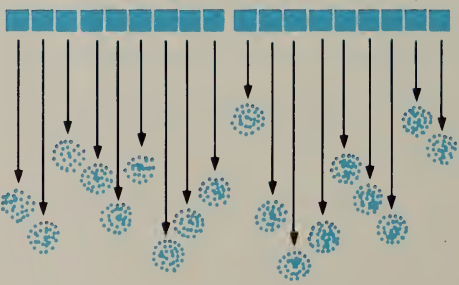


responses is to "switch off" the G protein, causing the message transmittal to stop.

The cell appears to employ this complex signaling system because it increases both the efficiency and speed of message transmission. A single incoming messenger molecule triggers a cascade of reactions that eventually results in a large amplification of the original message. Furthermore, the time elapsed between the arrival of a signal at a G protein and a cellular response is often only a few fractions of a second. For example, light-sensitive eye cells respond to as little as one photon of light in just a few milliseconds through a second messenger system. In contrast, other cells take as long as 30 seconds to respond to signals from the environment.

Certain diseases impair the functioning of the second messenger system, causing profound cellular malfunction. A toxin produced by the organism that causes cholera, for example, "locks" the G proteins of intestinal cells into the "on" position so that they are constantly stimulating the production of adenylate cyclase. This causes the cells to excrete vast amounts of fluid, accounting for the often-fatal diarrhea associated with cholera. In addition, because cell division is coordinated by a second messenger system, many researchers are now attempting to discern how a breakdown in this system might allow a cell to become cancerous.

How a signal brought to the cell by a single message molecule is amplified through the second messenger system.

Step	Action	Product
1. A message molecule binds to receptor and activates it.		
2. Each activated receptor activates many G proteins (two shown here), which each activate one molecule of the enzyme adenylate cyclase.		
3. Using ATP, each molecule of adenylate cyclase makes many molecules of cyclic AMP.		Cyclic AMP
4. Each cyclic AMP molecule makes one molecule of an enzyme called protein kinase.		Protein kinase
5. Each protein kinase molecule activates many molecules of some enzyme.		Enzyme "X" – varies depending on the protein kinase
6. Each copy of the activated enzyme produces many copies of its protein product.		Products of enzyme "X"

A Breakdown in the LDL System Can Now Be Treated

The low-density lipoprotein system works like a thermostat to ensure that the cell always has enough cholesterol for life and growth, without accumulating too much of it. Because of a defective gene, however, the cells of people with familial hypercholesterolemia (FH) are severely deficient in LDL receptors. This breaks the cells' normal chain of control and leads to over-production of cholesterol by the liver. The liver manufactures cholesterol and releases it into the blood, but since the cells do not have enough LDL receptors, not enough cholesterol is taken up. Instead it begins to clog the arteries.

People who have two genes for FH suffer from heart disease from a very early age, sometimes as early as age 1. Persons with only one defective gene do make some LDL receptors, but still have a high risk of heart attacks, and often have an attack before age 30. FH is a relatively common genetic disorder; as many as 1 person in 500 carries one copy of the defective gene.

Michael Brown and Joseph Goldstein of the University of Texas Health Science Center at Dallas elucidated both the precise genetic defects and the role of the LDL receptor in FH. In 1985, both men were awarded Nobel Prizes for this work. Their studies also led to the development of lovastatin, a drug to treat FH. Lovastatin has a dual action: it damps down the liver's ability to manufacture cholesterol so that fewer LDL's enter the bloodstream, and it causes the LDL receptors that the person has to take up cholesterol more efficiently.

The mechanism Brown and Goldstein outlined for LDL receptors is but one example of the process of receptor-mediated endocytosis. The cell also uses protein receptors to take in such substances as insulin, transferrin (an iron-bearing compound), and cell complexes that are produced when the immune system is activated.

A GLIMPSE OF THE FUTURE

In the three centuries since Robert Hooke turned his microscope on bits of dried cork, much has been learned about the world inside the cell. Directed by the genes and influenced by the environment, cells perform an astonishing array of tasks and take on a variety of forms suited to their work. Cell biologists now know a great deal about how the cell's living machinery works to make proteins, how many of the organelles are formed, and the steps involved in cell division. With so much revealed, it may seem that there is little mystery left in cells. But this is far from true.

Large portions of the cell's membranes, for example, remain uncharted territory. Although strides have been made in discerning the structure, function, and location of many surface and inner membrane proteins, studies of membrane lipids have lagged behind. In the years ahead, scientists will be attempting to discover how lipids in animal cells (which are manufactured at a single site, the endoplasmic reticulum) are transported to multiple sites throughout the cell.

Studies of cell organelles have been intense in recent decades, but much still remains to be learned about, for example, the actions of the Golgi apparatus and the endoplasmic reticulum. Protein receptors and trafficking signals that direct newly made proteins through these organelles have been postulated, but scientists have yet to isolate and characterize these systems. New techniques will probably be devised for examining the roles of cellular components, but there is still a place for such time-honored methods as cell fractionation, which was used by Paul Lazarow of The Rockefeller University and other investigators to separate peroxisomes from other cell components, thus fueling renewed interest in the study of this organelle.

In the future, isolated studies of cell organelles and molecules will be increasingly supplemented by investigations that aim to probe more global cellular functions. According to Norton Gilula of the Research Institute of Scripps Clinic, "the greatest single challenge in cell biology today is learning what regulates cell division and differentiation." How, for example, does each cell in a developing organism "know" when to turn the appropriate genes "on" or "off"? Why do some cells become "specialists," while others remain "generalists"? Why do normal cells eventually wear out and die—and what factors hasten or slow cell death?

To answer such questions, says Gilula, "we need to know not only details of shape and action for individual molecules, but also how these molecules interact in complete cells." Because the fundamental unit of an organism is the cell, whatever is learned about individual genes, proteins, and other molecules must be reinterpreted at the cellular level before a full understanding of the role of each in health and disease is possible.

Already, basic research on how cells

function has led to a variety of improvements in human health care. For example, an understanding of hormone release, binding, and action gained through the study of cellular models enabled pharmacologists to design a drug for high blood pressure. The drug works by selectively inhibiting the enzyme that normally allows blood pressure to rise.

Another area of basic cellular research that may lead to new therapeutic products is the study of angiogenesis, or blood vessel formation. Since tumors must be well vascularized in order to thrive, agents that inhibit angiogenesis might be employed to combat cancer. Conversely, agents that promote blood vessel growth might be useful as treatments for wounds and burns.

Finally, techniques that were originally developed to study genes and other cell components and to answer basic questions about cell activity are now being applied to medical problems, and offer great promise for the treatment of many illnesses. Technologies for fusing different cell types, for example, led to the development of "hybridomas"—antibody-producing cells fused with tumor cells. Hybridomas are living factories that produce large quantities of a single, specific antibody. These antibodies can detect, with great speed and accuracy, agents that cause such diseases as gonorrhea, hepatitis B, and AIDS.

"Cell studies," says Gilula, "form a bridge between what is known at the genetic level and what needs to be learned before new therapies can be developed." We are indebted to the scientists of the past who first revealed the marvels of the cell. As exciting as the past has been, however, the future promises to be still more thrilling as researchers begin to gain an even deeper understanding of cell activities and to apply that understanding to questions of health and disease.

GLOSSARY

Amino Acid—A building block of proteins. There are 20 different kinds of amino acids; a protein consists of a specific sequence of amino acids.

Angstrom—A unit of length, one hundred-millionth of a centimeter (approximately 0.000000004 inch); used for describing atomic dimensions.

Antibody—A protein produced by animals in response to an antigen (a foreign, often disease-causing, particle), which binds uniquely to the antigen.

ATP (adenosine triphosphate)—The compound that serves as a source of energy for the physiological reactions in cells.

Bacterium—A one-celled microorganism that contains no nucleus.

Base—The basic subunit of DNA or RNA. Paired bases—adenine with thymine and guanine with cytosine (uracil replaces thymine in RNA)— make up each "rung" of the "ladder" of the DNA molecule. See *nucleotide*.

Biochemistry—The study of the chemical reactions that occur in living organisms.

Cell—The basic subunit of any living organism; the simplest unit that can exist as an independent living system.

Cell Division—The doubling in mass and splitting of one "mother" cell into two "daughter" cells.

Cell Surface Membrane—A complex film of lipids interspersed with proteins. It covers the cell, maintains its integrity, and controls what goes in and what comes out.

Centrifuge—A machine that separates particles according to their size and density by spinning them at varying speeds.

Chloroplast—The chlorophyll-containing organelle in green plants in which light energy is converted into sugars.

Cholesterol—A waxy lipid produced by animal cells that is a prominent component of cell membranes.

Chromosome—A rod-shaped structure containing genes that is found in the cell nucleus. It is composed of DNA and proteins, and can be seen in a light microscope during some stages of cell division.

Codon—A sequence of three consecutive nucleotides in a DNA or RNA molecule that codes for 1 of the 20 amino acids in proteins or for a signal to start or stop protein production.

Cristae—The inward folds of a mitochondrion's inner membrane.

Cytoplasm—All the substance inside a cell, excluding the nucleus.

Cytoskeleton—A group of non-membrane-bound organelles that supports the cell. Some serve as conduits for the transport of various cell components.

Differentiation—The series of biochemical and structural changes that groups of cells undergo in order to form a specialized tissue.

DNA (deoxyribonucleic acid)—The substance of heredity; a large molecule that carries the genetic information necessary for all cellular functions, including the building of proteins. DNA is composed of the sugar deoxyribose, phosphate, and the bases adenine, thymine, guanine, and cytosine.

Electron Microscope—A powerful microscope that uses beams of high-speed electrons instead of light waves to illuminate objects for observation.

Endocytosis—The uptake of large molecules by the cell membrane. During this process, bits of the membrane fold inward and eventually pinch off to form small vesicles that move into the cytoplasm.

Endoplasmic Reticulum—An organelle made up of membranes that form a system of tubes and flattened sacs continuous with the nuclear membrane. Some of the membranes are smooth (the SER); others are "rough" (the RER) because they are dotted with ribosomes.

Enzyme—A substance (usually a protein) that speeds up, or catalyzes, a chemical reaction without being permanently altered or consumed.

Eukaryotic Cell—A cell that has a true nucleus surrounded by a membrane. This group includes all animal and plant cells, except blue-green algae.

Exocytosis—The movement of substances that are packaged in vesicles to the cell surface, where they fuse with the cell membrane and release their contents outside the cell.

Fluid-Mosaic Model—A model of the cell surface membrane in which proteins move about within a bed of semi-fluid lipids.

G Protein—One of a group of proteins involved in the second messenger system that bind to phosphate in order to pass along an incoming signal.

Gene—A unit of heredity; a segment of the DNA molecule containing the code for a specific protein product or function.

Glycolipid—A molecule composed of sugar and fat that forms an important component of cell membranes.

Golgi Apparatus—An organelle composed of membranous sacs that packages proteins into vesicles and sends them to the cell's surface or to lysosomes.

Intermediate Filament—A component of the cytoskeleton that acts to strengthen the cell.

Ion—Any atom or small molecule that contains an unequal number of electrons and protons and, therefore, carries a net positive or negative electrical charge.

Light Microscope—An instrument that magnifies objects using curved lenses and white light as a source of illumination.

Lipids—Fats and fat-like compounds.

Liposome—An artificial bubble made up of lipids that can contain substances, including drugs, designed to be absorbed by specific cells.

Lysosome—A small organelle containing powerful enzymes that can digest a variety of materials.

Microfilament—A threadlike organelle involved in cell motion, particularly muscle contraction.

Micrometer (or micron)—One one-thousandth of a millimeter; 10,000 angstroms; convenient for describing the dimensions of cells and organelles.

Microtubule—A thin, tubular organelle that acts as a structural support for the cell. During cell division, microtubules form the spindle that directs chromosomes to the daughter cells.

Mitochondrion—The cell organelle that converts the energy in sugars into ATP, thereby fueling the cell.

Molecule—The smallest physical unit of an element or compound. A molecule of an element consists of one or more identical atoms. A molecule of a compound consists of two or more different atoms.

Nanometer—One one-thousandth of a micrometer.

Nucleic Acid—Either of two kinds of molecules (DNA and RNA), formed by chains of nucleotides, that carry genetic information.

Nucleotide—A subunit of DNA or RNA. It includes one base, one phosphate molecule, and one sugar molecule (deoxyribose in DNA, ribose in RNA). See *base*.

Nucleus—In eukaryotic cells, the membrane-bound organelle that contains the genetic material.

Organelle—A specialized structure having a definite function in a cell; for example, the nucleus, a mitochondrion, a ribosome.

Peroxisome—A membrane-bound organelle that both generates and breaks down hydrogen peroxide.

Phospholipid—A fatty compound that contains phosphate. Phospholipids make up much of the outer membranes of cells and organelles.

Prokaryotic Cell—A cell that does not have a membrane around its nuclear region; for example, a bacterium.

Protein—A molecule made up of a number of amino acids arranged in a specific order determined by the genetic code. Proteins are essential for all life processes.

Receptor—A specialized molecule of a cell's membrane that receives information from the environment and conveys it to other parts of the cell. The information is transmitted in the form of a specific chemical that must fit the receptor like a key in a lock.

Replication—The duplication of hereditary material prior to cell division.

Respiration—Within cells, the breakdown of food molecules to liberate metabolically useful energy.

Ribosome—An organelle that contains RNA and protein, and is the site of protein synthesis.

RNA (ribonucleic acid)—A single-stranded nucleic acid that contains the sugar ribose. There are several forms of RNA, including messenger RNA, transfer RNA, and ribosomal RNA (all involved in protein synthesis), as well as several small RNA's whose functions are unclear. Certain viruses have RNA, instead of DNA, as their genetic material.

Second Messenger System—A multi-step signal amplification process used by the cell to transmit, for example, signals from many hormones that cannot enter the cell directly.

Transcription—The transfer of information from various parts of the DNA molecule to new strands of messenger RNA, which then carry this information from the nucleus to the cytoplasm.

Translation—The conversion of the genetic instructions for a protein from nucleotides of messenger RNA into amino acids.

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